Canadian Journal of PUBLIC HEALTH

VOLUME 35
NUMBER 9

TORONTO
SEPTEMBER, 1944

Antigenic Properties of Staphylococcus Enterotoxin

C. E. DOLMAN, M.B., B.S., M.R.C.P., D.P.H., PH.D. (LOND.)
Professor of Bacteriology and Preventive Medicine,
University of British Columbia, Vancouver;
Research Member, Connaught Laboratories (Western Division),
University of Toronto;
and Director, Division of Laboratories,
Provincial Board of Health of British Columbia

FROM the outset, the literature on staphylococcus entertoxin has been rather confusing and contentious. For instance, the importance of staphylococci as the potential cause of the commonest of all varieties of bacterial food poisoning has met increasing recognition in North America ever since the first report on the administration of filtrates to human volunteers by Dack, Cary, Woolpert and Wiggers (1). Yet in England the official viewpoint has been until lately that the large numbers of staphylococci often found in incriminated foodstuffs could usually be disregarded as irrelevant contaminants. Again, some of the earlier workers failed to distinguish clearly between alpha-toxin and enterotoxin effects in laboratory animals; and although Dolman (2) demonstrated ten years ago the separate identities of those two factors, Fulton (3) has recently claimed they are inseparable. On the other hand, Kojima and Kodama (4), Woodward and Slanetz (5) and others, found that filtrates containing beta-toxin gave positive cat or kitten reactions, and deduced that the enterotoxin was identical with beta-toxin. Dolman (6) has shown, however, using human volunteers, that these two factors are also entirely distinct; and that confusion between them had resulted from the fact that both toxins can evoke a feline vomiting reaction.

Based on a paper presented at the twelfth annual Christmas meeting of the Laboratory Section, Canadian Public Health Association, held in Toronto, December 15 and 16, 1943.

Viewed against this complicated background, discrepant reports appear inevitable on the more detailed properties of the enterotoxin, such as its solubility in chloroform and ether, its susceptibility to tryptic and peptic digestion, its precipitability by varying concentrations of ammonium sulphate, and its stability at different pH levels. But more fundamental than the foregoing points is the controversial question of the antigenicity of enterotoxin. This paper records experiments involving human subjects and cats, which appear definitely to indicate that enterotoxin is antigenic.

Literature

The peculiarly unpleasant effects of the enterotoxin no doubt account for the limited literature on attempts to demonstrate the acquisition of active immunity in man. Reports involving the use of laboratory animals have also, for various reasons, been sparse and rather inconclusive.

In the first record of authenticated staphylococcal food poisoning, Barber (7) noted that some inhabitants of the farm where the attacks occurred, who had regularly consumed the incriminated cow's milk, had acquired a slight resistance. But Barber and his associates gave themselves acute attacks several times without any apparent diminution in susceptibility. Dack, Jordan, and Woolpert (8) attempted to immunize human volunteers against the enterotoxin by administering, over periods up to 35 days, increasing daily dosages of toxic filtrates by mouth. Of their five subjects, two appear to have had a high degree of natural resistance or immunity, while the other three acquired little or no significant immunity to the homologous filtrate, and none to a heterologous filtrate. More recently, Dolman (6) has reported that three volunteers, who took enterotoxic filtrates by mouth, each suffered four severe reactions within periods of 4-6 months, without developing any apparent immunity.

Turning to experiments with laboratory animals, Woolpert and Dack (9) claim to have actively immunized a rhesus monkey by several subcutaneous injections of enterotoxic filtrate, but offer no evidence to show that it was initially susceptible. Serum from this monkey, and from a similarly immunized rabbit, failed to confer passive protection upon normal monkeys given enterotoxic filtrate by mouth. Dolman, Wilson and Cockcroft (10) reported that preliminary experiments pointed to the enterotoxin being antigenic, since kittens given successive intraperitoneal injections of enterotoxic filtrate became resistant. Subsequently, Dolman and Wilson (11) amplified this claim, and also stated that kittens showed passive protection when given intraperitoneally several minimal reacting doses of enterotoxic filtrate, mixed with cat, rabbit or horse serum from actively immunized animals. Minett (12) induced active immunity in kittens by subcutaneous injections of formalinized filtrate, and reported a moderate degree of passive protection exhibited by kittens given intraperitoneally mixtures of enterotoxin and serum from immunized rabbits. Again, Davison, Dack, and Cary (13) produced some degree of active immunity in monkeys by subcutaneous injections of enterotoxic filtrate. The serum of such monkeys passively protected kittens and a monkey, when mixed with

filtrate and injected intraperitoneally; but failed to confer protection when the mixtures were injected intracardially into kittens, or intravenously into monkeys. Finally, Weed, Michael, and Harger (14) briefly alluded to the active immunization of kittens given an enterotoxic filtrate subcutaneously.

While these reports suggest that the enterotoxin is at least slightly antigenic, this view has been seriously questioned by Hammon (15) on the grounds that results simulating the acquisition of specific immunity in kittens may actually be due to a low-grade peritonitis, and a consequently slow absorption rate, provoked by successive intraperitoneal injections of filtrate. Hammon admitted that even when enterotoxin was given intravenously to kittens, the minimal reacting dose increased after several injections; but he ascribed this phenomenon, despite its persistence for at least two months, to acquired tolerance. Using adult cats, and the intravenous route of administration, he found no definite neutralization of the enterotoxin by "hyperimmune" sera from cats and rabbits. Hammon's strong contention that enterotoxin is non-antigenic, and the realization that previous reports had not reckoned with the possibility of confusing the effects upon kittens of the definitely antigenic beta-toxin with those due to enterotoxin, seemed to reopen the issue. A few crucial experiments were therefore planned in order to settle the question.

Active Immunization of Human Volunteers

According to Dack, Jordan, and Woolpert (8), sub-minimal reacting doses of enterotoxic filtrate taken orally on many successive days failed to provoke any marked specific immunity in man; while Dolman (6) noted that volunteers given enterotoxin by mouth might suffer marked reactions on several occasions without apparently acquiring immunity. These reports discouraged further attempts at immunization by the oral route, and it was decided to employ a series of subcutaneous injections. In simple outline, the plan was first to establish an initial minimal reacting dose of enterotoxin for each subject; then to submit the group to a series of subcutaneous injections of suitably prepared filtrate derived from an enterotoxigenic strain; and finally, to determine what change, if any, had occurred in each individual's capacity to ingest enterotoxin without reaction.

Preparation of Filtrates

Whereas use of the oral route entails no necessity for special treatment of the filtrates to eliminate alpha- and beta-toxins (since these are not absorbed from the human gastro-intestinal tract), the subcutaneous route involves the taking of precautions to eliminate all alpha-toxin present, and to reduce any beta-toxin to a low titre, lest severe local and general reactions should follow the injections. Two methods of accomplishing this objective were adopted. One method was to add 0.5 per cent formalin to filtrates harvested from an enterotoxigenic strain grown on a soft agar medium for 40 hours at 37°C., in an atmosphere containing 30 per cent carbon dioxide. The formalinized filtrates

TABLE I

DEGREE OF RESISTANCE AGAINST INGESTED ENTEROTOXIN ACQUIRED BY HUMANS FOLLOWING SUBCUTANEOUS INJECTIONS OF FILTRATE 12069

Subject	Positive Reactions to Enterotoxin Before Immunization	Degree of Reaction	Total Immunizing Dosage; Dates of First and Last Doses	Maximum Amounts Taken without ill effect After Immunization
C.L.A.	**21:xi:42.** 2 cc. R_1 + 0.5 cc. alpha-antitoxic horse serum	Vomited 9 times; diarrhoea moderate	0.47 cc. in 5 injections. **14:vii:43–2:viii:43**	
M.R.D. = 1.5 cc.	**12:ii:43.** 10 gm. sausage infected with strain 12069 alpha	Vomited 6 times; diarrhoea marked		**12:viii:43.** 3.0 cc. L_4
	19:ii:43. 10 cc. extract of sausage infected with strain 12069 alpha	Vomited 8 times; diarrhoea violent		**1:xii:43.** 3.0 cc. L_4
			1.5 cc. in 10 injections, **28:iii:44–31:v:44**	
	5:iv:43. 2 cc. R_1 + 8 cc. serum from naturally immune human	Vomited 10 times; diarrhoea violent		**6:vii:44.** 7.5 cc. A_7*
	13:vii:43. 1.5 cc. L_4	Vomited 4 times; nausea for 10 hrs.		
H.C.	**18:v:42.** 1 cc. R_1	Vomited 6 times; marked cramps.	0.18 cc. in 4 injections, **21:xi:43–3:xii:43**	
M.R.D. = 0.75 cc.	**21:xi:43.** 0.75 cc. A_5	Vomited 8 times; diarrhoea marked		**9:xii:43.** 1.5 cc. A_5
				12:xii:43. 2.0 cc. A_5 (Vomited once)
			0.9 cc. in 8 injections, **1:iv:44–30:v:44**	**29:vii:44.** 5.0 cc. A_7
C.E.D.	**20:v:42.** 3 cc. R_1	Vomited 5 times; diarrhoea violent	0.2 cc. in 4 injections, **14:vii:43–2:viii:43**	
M.R.D. = 1.5 cc.	**22:vii:42.** 1.5 cc. R_1 + 0.75 cc. beta-antitoxic horse serum	Vomited once		**12:viii:43.** 3.0 cc. L_4
			0.18 cc. in 4 injections, **22:xi:43–3:xii:43**	**21:xi:43.** 3.0 cc. L_4
	21:xi:42. 1.5 cc. R_1 + 0.3 cc. alpha-antitoxic horse serum	Vomited 5 times; diarrhoea violent		**7:xii:43.** 5.0 cc. A_5
	19:ii:43. 10 cc. extract of sausage infected with strain 12069 alpha	Vomited 5 times; diarrhoea violent		**9:vii:44.** 6.5 cc. A_7
	14:vii:43. 1.25 cc. L_4	Yawning, salivation, and nausea		

Filtrates R_1, L_4, A_5 and A_7 all prepared from strain 12069: filtrate H from a separate strain.

*Potency of filtrate A_7 verified on subject R.R. (*vide infra*), and also on subject L.E.R., who vomited 11 times, with marked diarrhoea, and required several days to recover, after taking 0.75 cc. on **6:vi:44.** Same subject vomited 4 times, with moderate diarrhoea, after taking 1.0 cc. R_1 on **18:v:42;** and had sneezing, nausea, cramps and mild diarrhoea after taking 0.5 cc. L_4 on **9:vii:43.**

TABLE I—(Continued)

TABLE I—(Continued)

Subject	Positive Reactions to Enterotoxin Before Immunization	Degree of Reaction	Total Immunizing Dosage: Dates of First and Last Doses	Maximum Amounts Taken without ill effect After Immunization
U.D.	**21:xi:43.** 0.75 cc. A_5	Nausea, abdominal discomfort and cramps; diarrhoea intermittently for 36 hours	0.17 cc. in 4 injections, **22:xi:43–4:xii:43** 0.82 cc. in 8 injections, **12:iv:44–20:vi:44**	**12:xii:43.** 2.0 cc. A_5 **9:vii:44.** 3.0 cc. A_7 **23:vii.44.** 4.0 cc. A_7 (Abdominal discomfort, cramps and slight nausea) **3:ix:44.** 4.0 cc. A_7 (Slight abdominal discomfort and cramps, one loose stool)
R.L.H.	**18:v:42.** 1 cc. R_1 **21:vii:42.** 1 cc. R_1 **30:vii:42.** 1 cc. R_1 **15:ix:42.** 1 cc. H **22:i:44.** 0.75 cc. A_5 **29:i:44.** 1.0 cc. A_5 **26:ii:44.** 1.25 cc. A_5	Vomited 8 times Vomited 16 times; diarrhoea moderate Vomited 10 times Vomited twice; diarrhoea violent Abdominal cramps, nausea and diarrhoea Nausea and general malaise Severe vomiting and diarrhoea intermittently for 48 hours	1.5 cc. in 10 injections, **28:iii:44–31:v:44**	**28:vi:44.** 4 cc. A_7 **30:viii:44.** 5 cc. A_7
D.E.K.	**13:viii:43.** 1 cc. L_4	Continuous vomiting and diarrhoea for 3½ hours.	0.18 cc. in 4 injections, **20:xi:43–2:xii:43** 0.9 cc. in 8 injections, **1:iv:44–30:v:44**	**10:xii:43.** 2.5 cc. A_5 **12:xii:43.** 3.0 cc. A_5 (Marked vomiting and diarrhoea) **16:vi:44.** 2.5 cc. A_7 (Nausea) **18:vi:44.** 2.75 cc. A_7 (Vomited 14 times)
R.R.	**18:v:42.** 1 cc. R_1 **6:vi:44.** 1 cc. A_7	Vomited 7 times; diarrhoea moderate Vomited 6 times	1.2 cc. in 4 injections, **30:vi:44–13:vii:44**	**1:viii:44.** 5.0 cc. A_7

were then incubated at 37°C. until no rabbit cell haemolysin remained.* To help maintain bacteriostasis, 1:10,000 merthiolate was added, and the material was released for use after passing the usual sterility tests.

The other method took advantage of the fact that this particular strain, when grown on soft agar in air at room temperature (about 20°C.) for 3½ days, produced only negligible traces of alpha-toxin; whereas the enterotoxic potency of the filtrates was as consistently high as when the more customary method, described above, was used. This method has proved simple and satisfactory for the routine production of large batches of enterotoxin from strain 12069 alpha. Filtrates prepared thus are injectable into cats and other laboratory animals without preliminary treatment. If it could be shown that under these room-temperature conditions all, or even many, enterotoxigenic strains produced detectable amounts of enterotoxin, with negligible amounts of alpha- and beta-toxins, the method would present obvious advantages for laboratories called upon to identify food-poisoning strains of staphylococcus. All the filtrates used for oral administration to humans in these experiments were prepared by this method. However, when subcutaneously injected, one such filtrate showed a tendency to cause more marked local and general reactions than did a formalinized filtrate prepared in the usual way. The latter type of preparation was therefore chiefly used for injection of humans (*vide infra*).

Determination of Initial Susceptibility

The minimal reacting dose of filtrate for each of seven volunteers was carefully determined before immunization by giving as little as 0.5 cc. in some instances, and never more than 1.0 cc., as a trial dose by mouth. For two persons, 0.75 cc. of filtrate sufficed to cause a severe enterotoxic reaction; and an initial dose of 1.0 cc., taken by another person, led to so violent a reaction that it seems likely 0.75, or even 0.5 cc., would have proved sufficient. When no reaction occurred, the dose was increased by 0.25 or 0.5 cc., and administered one or more days later. Only two subjects in this experimental group proved initially able to take more than 1.0 cc. Their minimal reacting dose, just prior to immunization, was about 1.5 cc.; but both of them had taken larger doses, with correspondingly severe reactions, at an earlier stage of investigation into enterotoxin in this laboratory, when it was not realized how small an increment in dosage might change the reaction from negative to positive. The results of these preliminary tests are set forth in the first two columns of Table 1. On two persons (U.D. and D.E.K.) only one determination of minimal reacting dose was made; two others (H.C. and R.R.) each took enterotoxin on two occasions, separated by 1½ and 2 years respectively; while the other three participants suffered 5-7 reactions of varying degrees over periods ranging from 8 to 23 months. In addition to those doses listed

**The strain of staphylococcus used throughout these experiments on humans was 12069 alpha, whose origins and properties have been previously described in detail by Dolman (6). Filtrates prepared therefrom contained no detectable beta-toxin; but future workers may find the suggestion helpful that staphylococcal filtrates should not be released for injection into man if their beta-toxin titre exceeds 100 hot-cold sheep cell haemolytic units per cc.*

as giving definite reactions, nearly every member of the group took one or more smaller, ineffective amounts.

When due allowance has been made for slight losses of potency by a given preparation as a result of storage, and also for minor differences in potency between the various batches of filtrate used, the minimal reacting dose seems to have remained remarkably constant for each person who took enterotoxin on multiple occasions.* This fact not only further illustrates the failure of repeated oral consumptions of filtrate to induce active immunity, but also gives validity to the assignment of a certain initial minimal reacting dose to two of the participants on the basis of a single positive reaction.

The degree of reaction accepted as positive ranged from definite nausea, with a few loose stools, to a prolonged series of bouts of severe vomiting and diarrhoea. Such marked reactions occurred in two or three instances where inadvertently the dose taken was probably larger than minimal. One person (R.L.H.) whose minimal reacting dose remained around 1.0 cc. despite six positive reactions over a period of 20 months, took 1.25 cc. just before going to bed. Nothing occurred until he rose nearly 10 hours later, when vomiting and diarrhoea began, and continued (save for one interval of a few hours) for over 48 hours. Reference is made here to this particular reaction because it clearly suggests that the incubation period in staphylococcal food poisoning may occasionally be prolonged beyond the commonly accepted 2-5 hours. In other words, an apparent incubation period of 6-12 hours in a food-poisoning outbreak is not alone sufficient to exclude staphylococci from consideration as the possible cause, particularly when very few persons are involved.

Immunization Procedure

All injections were given subcutaneously in the upper arm, the usual intervals between doses being 4-7 days. At the outset, as little as 0.025 cc. of filtrate from a 3½-day room-temperature culture of strain 12069 alpha gave a marked local and a severe general reaction to one male volunteer. Six hours after the injection, there was a prolonged chill, followed by a temperature rising to 103.6°F., tachycardia, backache, anorexia, and general malaise. He took to bed for 36 hours, and for some days after had joint pains and felt unwell. Of two others receiving the same dosage, a male subject had a marked local and moderate general reaction; while a female subject had an equally marked local, but no general reaction. These reactions were attributed to some staphylococcal autolysate whose production was encouraged by the rather long period of growth prior to filtration. The two subjects who suffered lesser reactions (C.L.A. and C.E.D.) received a series of 5 and 4 small injections of this filtrate, and acquired some immunity therefrom. All injections subsequently administered to them and to their associates were of the formalinized filtrate prepared from 40-hour growth at 37° C., and the resulting reactions were negligible.

**Such dosages as e.g. 10 cc. extract of sausage infected with strain 12069 alpha obviously cannot be estimated accurately in terms of enterotoxic filtrate, and are inserted only to complete the list of definite reactions experienced by those concerned. The significance of these particular dosages may be found in a previous report (6).*

The total dosages of filtrate given subcutaneously to each subject, with the dates of the first and last injections, are shown in the fourth column of Table 1. In most instances, the initial dose of the series was 0.01 cc., and the largest was 0.25 cc. However, one person (R.R.) who was erroneously given 0.2 cc. as a first dose, and suffered no undue reaction therefrom, received 0.4 cc. two weeks later as the last of a series of 4 injections totalling 1.2 cc. of filtrate. Five of the subjects received two series of injections, separated by an interval of several weeks. The maximum total amount of filtrate received subcutaneously (Subject C.L.A.) was 1.97 cc., divided into 15 injections over a period of 10 months; and the minimum total amount (Subject C.E.D.) was 0.38 cc., given in 8 injections over a period of nearly 5 months.

Test for Immunity Development

Within a few days of completing their series of injections the subjects took by mouth amounts of enterotoxic filtrate corresponding to their respective initial minimal reacting doses. No reaction occurred in any instance. Accordingly, next day, or as soon thereafter as suited the subject's convenience, the amounts were increased by 0.5 cc., and were again taken by mouth without effect. This procedure was continued, increasing the dosage each time by 0.5-1.0 cc., until either the victim had an enterotoxic reaction, or the instigator had qualms about going further. In some instances, as a test for persistence of the immunity, another series of doses of filtrate, culminating in the same or even a higher maximum dose, was consumed several weeks or months after immunization.

As far as possible, the doses of enterotoxin taken by each subject before and after immunization were from the same batch of filtrate. When recourse to different batches was unavoidable, care was taken to ensure that the preparations used in tests for immunity development were not less potent than those used in the determinations of initial minimal reacting dose. The potency of each new batch was verified by evoking an enterotoxic reaction in at least two susceptible persons with an oral dose of 1.0 cc. or less. Further assurance that the batches were of equivalent potency was gained by demonstrating the same average minimal reacting dose among groups of several cats injected intravenously with 1-3 cc. amounts of each batch. The stability of the enterotoxin is such that loss in potency of filtrates stored in the refrigerator for even several months may be discounted as a significant source of error.

Summary of Results

The figures given in the last column of Table 1 represent the maximum amounts of filtrate consumed by each subject shortly after a given series of injections. These amounts were taken without any ill effect, except where a reaction is specifically mentioned. The maximum amounts taken in the few tests for persistence of immunity have also been listed. The extent of immunity developed in each subject may be briefly summarized as follows:

C.L.A. (♀) Initial M.R.D. 1.5 cc. Ten days after 5 injections of filtrate, totalling

0.47 cc., and given in 9 days, took 3.0 cc. by mouth without effect. Took 3.0 cc. again 3½ months later without effect. About 4 months later, began another series of 10 injections, totalling 1.5 cc., and spaced over 2 months. Five weeks after completing this second course of injections, took 7.5 cc. by mouth without effect. This subject acquired an immunity to over *five* times the dosage which had originally caused a severe enterotoxic reaction.

H.C. (♀) Initial M.R.D. 0.75 cc. Six days after 4 injections of filtrate, totalling 0.18 cc. and given in 12 days, took 1.5 cc. by mouth without effect. Three days later, 2.0 cc. caused a mild enterotoxic reaction. Four months later, began another series of 8 injections, totalling 0.9 cc. and spaced over 2 months. Five weeks after completing this second course of injections, took 4.0 cc. of filtrate, and two months after completing the course, took 5.0 cc., without effect. This subject acquired an immunity to over *six* times the dosage which had originally caused a severe enterotoxic reaction.

C.E.D. (♂) Initial M.R.D. 1.5 cc. Ten days after 5 injections of filtrate, totalling 0.2 cc., and given in 19 days, took 3.0 cc. by mouth without effect. Took 3.0 cc. again nearly 3½ months later without effect. At that time began another series of 4 injections, totalling 0.18 cc., and spaced over 11 days. Four days after completing this second course of injections, took 5.0 cc. of filtrate without effect. Seven months later, took 6.5 cc. of filtrate without effect. This subject maintained, for at least seven months, an immunity to over *four* times the dosage which had previously caused severe enterotoxic reactions.

U.D. (♀) Initial M.R.D. 0.75 cc. Eight days after 4 injections of filtrate, totalling 0.17 cc., and given in 12 days, took 2.0 cc. by mouth without effect. Four months later, began another series of 8 injections, totalling 0.82 cc., and spaced over 10 weeks. About 3 weeks after completing this second course of injections, took 3.0 cc. of filtrate without effect. One month after completing the course, took 4.0 cc. of filtrate, and a very mild enterotoxic reaction resulted. Six weeks later, repeated this 4.0 cc. dose, with a similar result. This subject acquired an immunity to roughly *five* times the dosage which had originally caused a moderate enterotoxic reaction.

R.L.H. (♂) Initial M.R.D. 1.0 cc. Four weeks after 10 injections of filtrate, totalling 1.5 cc., and spaced over 2 months, took 4.0 cc. by mouth without effect. Two months later, took 5.0 cc. of filtrate without effect. This subject acquired an immunity to over *five* times the dosage which had previously caused severe enterotoxic reactions.

D.E.K. (♀) Initial M.R.D. 1.0 cc. Eight days after 4 injections of filtrate, totalling 0.18 cc. and given in 12 days, took 2.5 cc. by mouth without effect. However, 3.0 cc. taken two days later caused a severe enterotoxic reaction. About 3½ months later, began another series of 8 injections, totalling 0.9 cc. and spread over 2 months. Sixteen days after completing this second course of injections, took 2.5 cc. of filtrate, and had a mild enterotoxic reaction. Two days later, took 2.75 cc. of filtrate and had a severe reaction. This subject acquired an immunity to roughly 2½ times the dosage which had originally caused a very severe enterotoxic reaction.

R.R. (♂) Initial M.R.D. 1.0 cc. Nineteen days after 4 injections of filtrate, totalling 1.2 cc. and given in 13 days, took 5.0 cc. by mouth without effect. This subject acquired an immunity to over *five* times the dosage which had previously caused severe enterotoxic reactions.

If we exclude subject D.E.K., these results may be summarized by the statement that 3 men and 3 women were able to ingest without effect, on the average, five or more times the amount of enterotoxin which had evoked a definite reaction prior to their receiving several subcutaneous injections of an enterotoxic filtrate. The assumption may reasonably be made, in view of the particularly violent initial reaction of subject D.E.K. to 1 cc. of filtrate, that her true minimal reacting dose was at that time 0.75 cc., or even less. In this event, her degree of acquired immunity does not fall far short of that shown by the others in the group.

Comments on Results

Ideally, these experiments would have been performed with a single, completely stable preparation of enterotoxin. But the unavailability of such a preparation does not significantly affect the interpretation of the results, for reasons already given. Again, the number of participants is admittedly small; but the nature of the enterotoxic reaction in man precluded any larger-scale experiment along these lines. The responses of the 7 volunteers have been given in sufficient detail for critical analysis, and are believed entirely consistent with the claim that enterotoxin is antigenic. Attention is particularly drawn to the increased resistance to enterotoxin of 6 persons after 4-5 injections given in only 12-19 days; to the considerably higher level of acquired resistance shown by one subject (H.C.) after a second series of injections; and to the verified maintenance of acquired resistance by several subjects for periods ranging from a few weeks up to seven months after completion of their series of injections. Even the lesser degree of resistance developed by subject D.E.K., as compared with the others, and her apparent failure to respond at all to the second series of injections, exemplify a familiar immunological phenomenon. Incidentally, the extent of resistance to enterotoxin shown by the various individuals was not related at any stage of the experiment to their titres of circulating alpha-antitoxin, or to the capacities of their sera to neutralize the beta-toxin. In sum, these results cannot be satisfactorily explained except in terms of the provocation of specific antibodies to the enterotoxin by the subcutaneous injections of enterotoxic filtrate.

Active Immunization of Cats

The results of numerous experiments carried out on cats strongly support the above conclusions. The usual difficulties were encountered in securing cats and maintaining them healthy for laboratory purposes. Careful attention to diet, the use of feline anti-distemper vaccine and serum, and the segregation of adult cats from kittens, proved important measures in ensuring a supply of cats which could be kept under test, when necessary, for many weeks or months. Most of the filtrates used in this work with cats were prepared by the 3½-day room-temperature method from strain 12069 alpha. After Seitz filtration, such filtrates could be injected intravenously without further treatment. Although no reactions occurred which could be attributed to alpha- or beta-toxins, cats occasionally showed transitory shock immediately after injection, with profuse salivation, panting respirations, tachycardia and collapse. Such reactions were more usual among cats previously injected with enterotoxin, but in one or two instances the same behaviour was shown by a normal cat. Recovery was usually complete within a few minutes, although very rarely prolonged or even fatal shock occurred. This type of reaction was attributed to a bacterial autolysate, or to some component of the medium, to which certain cats were hypersensitive. Any cat exhibiting shock sufficient in degree or duration to mask a possible enterotoxic reaction was eliminated from experimental protocols.

In comparison with man, the cat is highly resistant to enterotoxin. This fact rendered infeasible the oral route of administration. The intravenous route was chosen in order to avoid the possible fallacy alleged by Hammon (15) to derive from use of the intraperitoneal route. Adult cats or large kittens were selected, partly because of their lesser liability to fatal infections adventitiously contracted during the course of the experiment, and partly because their susceptibility to the enterotoxin proved on the whole higher and more consistent than that of young kittens.

Preliminary trials had shown that the degree of immunity developed by some cats was comparatively small, and might not be evident unless the initial minimal reacting dose had been fairly accurately determined for each test animal. Such determinations presented the obvious difficulty that every tentative dose, whether too large or too small, was liable to affect the immunity level. However, accumulating experience with a given filtrate soon furnished some clue as to its probable minimal reacting dose for a cat of given weight. Properly prepared filtrates from strain 12069 alpha usually provoked a typical reaction in normal cats of 1-3 kg. weight in a dosage of 1-2 cc. intravenously.

Subsequently the cats were repeatedly injected at varying intervals with gradually increasing doses of enterotoxin. Usually at least 2-3 days elapsed between doses, to permit the animal to recuperate fully, while sometimes the interval was several days or even weeks. Some idea of the approximate rate and degree of the immunity development could thus be gained. The types of results obtained may be illustrated by summarizing the treatment and reactions of 3 cats, representative of some 12 kittens and cats in whom the development of active immunity was thus traced.

"*Large White*," weight 2680 gm. Had marked reaction following initial injection of 2.0 cc. of filtrate A_1.* Four weeks later received 2.0 cc. without effect, having meanwhile had 4 marked reactions to amounts of A_1 ranging from 2.1 to 3.0 cc. Three months after first injection received 4.0 cc. A_1 without effect, but gave borderline reaction to 5.0 cc. after having 17 intravenous injections of amounts ranging from 2.0 to 3.5 cc., to 13 of which there had been a marked reaction. Even assuming the true initial minimal reacting dose for this cat to have been nearer 1 cc. than 2 cc., it required 17 injections, totalling 55 cc. of enterotoxin, and given over a period of 3 months, to provoke an immunity to *2½-5* times the initially effective dose.

"*Tabby*," weight 3155 gm. Reacted to first injection of 1.5 cc. of filtrate A_5. Three days later reacted to 1.2 cc. A_5. Next day received 1.0 cc. A_5 without effect. Thereafter received 5 increasing doses, each without effect, until one month after commencement of immunization was able to resist 3.6 cc. A_5. Without further intervening dosage, given 5.0 cc. A_7 five months after the first injection, and one week later given 6 cc. A_8, without effect. One month later, again given 6.0 cc. A_8 without effect. This cat developed an immunity to at least *3* times the initial minimal reacting dose after receiving 6 injections totalling 12.6 cc., and given in one month; and later increased its immunity to at least *5* times the initial minimal reacting dose, after receiving a total of 29 cc. of enterotoxin in 11 injections, given over a period of 5 months.

"*Mr. Smith*," weight 2640 gm. Had marked reaction following 1.2 cc. A_5. After 4 intervening doses, all ineffective, took 5.0 cc. A_5 without effect about one month after the initial dose. This cat developed an immunity to at least *4* times the initial minimal reacting dose, following 6 injections totalling 16.4 cc., and given over a period of one month.

**Filtrates A_1, A_5, A_7 and A_8 were of approximately equal potency.*

These examples point to wide variations in the capacity of cats to produce antibodies in response to intravenous injections of enterotoxin; and also indicate that, in general, cats require relatively enormous doses of enterotoxin intravenously in order to acquire an immunity of the same order as that shown by man after only a few small subcutaneous injections. The possibility that the intravenous route is especially unsatisfactory for the immunization of cats against enterotoxin seems discounted by the failure of several attempts to demonstrate other than minor degrees of acquired immunity in cats given a series of small subcutaneous injections. Since the results in human beings hardly suggest that enterotoxin is an inefficient antigen, it must be supposed that for some reason cats are poor manufacturers of anti-enterotoxin. It is noteworthy that this characteristic should be associated with a naturally high resistance of the feline vomiting centre to the action of enterotoxin. Conjecture aside, the relevant feature of these results with cats is that they confirm the antigenicity of the enterotoxin.

Cross-Immunity in Cats against Heterologous Enterotoxin

The actively immunized cats described above presented an opportunity to test for cross-protection against enterotoxins of different strain origins.

Filtrates were prepared by the 3½-day room-temperature method from 3 strains of enterotoxigenic staphylococcus, two isolated from hams, and one from potato, incriminated in food-poisoning outbreaks. The potency of each filtrate was verified by obtaining marked enterotoxic reactions on injecting the following amounts intravenously into normal cats or kittens:—2.5 cc. filtrate from strain Ham into 1200 gm. kitten; 5 cc. filtrate from strain Potato 54 into each of 2940 gm. and 2770 gm. cats; and 5 cc. filtrate from strain Ham F into 3100 gm. cat. With intervals of a few days between doses, 3 cats previously immunized against filtrate from strain 12069 alpha, and of comparable weight to the foregoing controls, received intravenously 5 cc. of filtrate from each of the 3 above-described strains. The immunized cats gave no enterotoxic reaction whatever against these heterologous filtrates.

These findings indicate that staphylococcus enterotoxin is probably a single qualitative entity. The following examples of passive immunity support this claim, and also supply further evidence of the antigenicity of enterotoxin.

Neutralization of Enterotoxin by Immune Serum

Blood serum was available in the laboratory from humans, cats and rabbits injected with enterotoxic filtrate from strain 12069 alpha; and also from two horses which had been intensively immunized with filtrates from another enterotoxigenic strain ("Barss"), and a non-enterotoxigenic strain ("24"), respectively. If the acquired resistance to enterotoxin developed by the treatment described above were due to the usual type of active immunity, specific circulating antitoxin should be demonstrable in the immunized animals. Several experiments were carried out to verify this point. The presence of appreciable amounts of antitoxin in a given serum was deemed indicated when no reaction followed the intravenous injection into a cat or large kitten (of subsequently proven susceptibility) of a normally effective dose of enterotoxin,

mixed with a suitable amount of the serum under test. These neutralization tests were carried out as follows:

The test serum was added to a suitable amount of the enterotoxic filtrate, the mixture left at 37°C. overnight, and an appropriate volume then injected into a normal cat. Each animal received first a mixture containing the supposedly immune serum, and a few days later, to prove its susceptibility, was given an equivalent dose of enterotoxin mixed with non-immune serum.

Typical examples of the results obtained are shown in Table II. Two cc. of serum from an immunized human subject, and also from an immunized rabbit, neutralized 3.5 cc. of enterotoxin, whereas the same volume of non-immune human and rabbit serum had no apparent neutralizing capacity. A similar phenomenon was shown by cat "Gray Dawn", successively given mixtures of enterotoxin with serum from an immunized and a normal cat. But the volumes of serum and enterotoxin were here reversed, since proportionately lesser amounts of immune cat serum had failed occasionally to give protection—a fact which again illustrates the rather low titre of circulating anti-enterotoxin developed by some cats. Again, cat "Molly" showed that 0.5 cc. of "Barss" horse serum neutralized 3.5 cc. of heterologous enterotoxin, whereas 2.0 cc. of "24" horse serum failed to neutralize this amount of enterotoxin. Incidentally, the alpha-antitoxin content of serum "24" was higher (150 standard units per cc.) than that of serum "Barss" (135 standard units per cc.), which may be adduced as yet another point rendering completely untenable Fulton's suggestion that the alpha-toxin and enterotoxin are closely related, if not identical.

Bearing in mind that each of the results tabulated is representative of several others actually performed, these experiments suggest that enterotoxin is an orthodox antigen, in that when repeatedly administered parenterally to man and certain laboratory animals, a detectable increase in specific circulating antitoxin generally results. Unfortunately, the limited cat supply precluded attempts to titrate and compare the neutralizing capacities of various immune sera; but the method described might well be adapted to quantitative assay if large numbers of cats were procurable.

TABLE II

NEUTRALIZATION OF ENTEROTOXIN BY SERUM FROM IMMUNIZED HUMAN, CAT, HORSE AND RABBIT

Cat Designation and Weight	Material Injected	Reaction
"Pest" (1150 gm.)	3.5 cc. A_8 + 2.0 cc. serum from immunized human C.L.A.	Nil
	3.5 cc. A_8 + 2.0 cc. serum from non-immunized human	Vomited, at 11′, 40′, 48′, 52′ and 57′; loose stool at 49′
"Gray Dawn" (1425 gm.)	2.0 cc. A_8 + 3.5 cc. serum from immunized cat	Nil
	2.0 cc. A_8 + 3.5 cc. normal cat serum	Vomited at 94′
"Molly" (2770 gm.)	3.5 cc. A_8 + 0.5 cc. anti-enterotoxic horse serum "Barss"	Nil
	3.5 cc. A_8 + 2.0 cc. horse serum "24"	Vomited at 38′; watery stool at 45′
"Farm Black" (1140 gm.)	3.5 cc. A_8 + 2.0 cc. serum from immunized rabbit	Nil
	3.5 cc. A_8 + 2.0 cc. normal rabbit serum	Vomited at 28′

A_8 was a filtrate from strain 12069 alpha grown for 3½ days at room temperature.
All sera were inactivated by heating at 56°C. for 30 minutes, and the serum-toxin mixtures left at 37°C. overnight.

Discussion

The apparently conclusive evidence submitted in this report, that staphylococcus enterotoxin is antigenic, encourages the hope that some serological method, e.g. a flocculation test, might eventually become available for the detection and titration of this factor. The maintenance of a cat colony presents many serious problems, while recourse to human volunteers is a most unsatisfactory alternative. Dolman and Wilson (11) described flocculation reactions between enterotoxic filtrates and absorbed horse serum; but the preliminary treatment required by their reagents, and the frequent appearance of multiple zones, were formidable complications. The room-temperature method of preparing enterotoxin from strain 12069 alpha might facilitate production of an almost monovalent anti-enterotoxic horse serum of high potency and suitable flocculating properties. Studies along these lines are proceeding.

Many workers have attempted the separation and purification of enterotoxin by physico-chemical methods, without apparent success. Its relative heat stability, and its failure to traverse a dialysing membrane (two properties about which there seems general agreement) suggest that the isolation of enterotoxin in a purified state should present no insuperable difficulties. Settlement of the doubt as to its antigenicity is an obvious prerequisite to this type of work, since the final proof of identity of an alleged preparation of purified enterotoxin would necessarily entail verifying its possession of the appropriate pathogenic and antigenic properties.

Some criticism may be levelled at the failure to determine the limits of the active immunity developed by the volunteers. But reference to Table I will recall that the final trial doses gave reactions in 2 of the 7 subjects, and it seems unlikely that the other subjects could have consumed with impunity much larger doses than those actually taken. Moreover, temerity weakened as the dose enlarged—despite the fact that when enterotoxic reactions were provoked in 3 partially immunized subjects (H.C., U.D., and D.E.K.) these were milder than those suffered from smaller doses prior to immunization. In any event, when investigating the value of an antigen in humans, it is not customary to test the limitations of the acquired immunity by deliberating exposing it to increasing strain until resistance is broken. The main objective in active immunization is to confer resistance against specific hazards of a degree ordinarily encountered. The acquisition of resistance by several experimental subjects to at least 5 times their initial minimal reacting doses of enterotoxin, points to the possibility of providing protection against the more usual chances of staphylococcal food poisoning. Indeed if in due course this enhanced resistance should prove sufficiently persistent, good arguments could be presented in favour of widespread immunization against the enterotoxin.

A final comment seems warranted on the interesting fact that although enterotoxin is readily absorbed from the human gastro-intestinal tract, and thence reaches the vomiting centre, presumably via the blood stream, no effective stimulus to specific antibody formation appears to result. The fact that this antigen, whose normal portal of entry into the body is the gastro-intestinal

tract, fails to provoke immunity when repeatedly absorbed by that route, makes it improbable that oral administration of antigens not normally absorbed through the gastro-intestinal tract could result in any significant development of specific antibodies.

Summary

1. By growing a food-poisoning strain of staphylococcus on a soft agar medium for 3½ days at 20°C., filtrates were obtained having a high enterotoxic potency, but no titratable alpha- or beta-toxin content.

2. Such filtrates could be injected intravenously into cats without further treatment, and no unduly marked local or general reactions occurred in two humans given a few small doses subcutaneously. However, another subject had a severe reaction following subcutaneous injection of 0.025 cc. of untreated filtrate.

3. A filtrate prepared from the same strain grown for 40 hours at 37°C. in an atmosphere containing 30 per cent CO_2 was incubated with 0.5 per cent formalin until no alpha- or beta-toxin was detectable. Seven persons received subcutaneous injections of this filtrate in amounts ranging from 0.01 cc. to 0.4 cc., with negligible resulting reactions.

4. The resistance of 3 men and 3 women to enterotoxin taken by mouth was increased on the average at least 5-fold, following either one or two series of injections of formalinized enterotoxic filtrate. Another female subject showed a somewhat lesser degree of acquired resistance. This increased resistance was maintained by some persons for several weeks, and in one instance was demonstrably still present 7 months after the last injection of filtrate.

5. Cats and large kittens given repeated intravenous injections of enterotoxin were eventually able to withstand several times their initial minimal reacting doses; but they developed resistance far less readily than did human subjects.

6. Cats thus rendered resistant showed cross-protection against enterotoxic filtrates of heterologous strain origin.

7. Specific neutralization of the enterotoxin by serum from immunized human and animal sources was demonstrated by injecting enterotoxin-serum mixtures intravenously into cats.

8. The results obtained are consistent only with the conception that staphylococcus enterotoxin is an antigenic entity.

Acknowledgments

I wish to acknowledge the valuable help given by Miss C. L. Aszkanasy at certain stages of this investigation. Misses A. Sandison and M. McKenty and Messrs. W. G. B. Casselman and G. M. Fierheller have also assisted in various ways. I am indebted to the Associate Committee on Medical Research of the National Research Council of Canada for a grant which has recently facilitated the work. Finally, special thanks are due to those who volunteered to take the filtrates, overlooking inconvenience and stifling apprehension in an endeavour to help settle a problem.

References

(1) Dack, G. M., Cary, W. E., Woolpert, O., and Wiggers, H.: J. Prev. Med., 1930, *4*:167.
(2) Dolman, C. E.: J. Infect. Dis., 1934, *55*:172.
(3) Fulton, F.: Br. J. Exper. Path., 1943, *24*:65.
(4) Kojima, T., and Kodama, T.: Kitasato Arch. Exper. Med., 1939, *16*:197.
(5) Woodward, J. M., and Slanetz, L. W.: J. Bact., 1941, *42*:817 (Abstract).
(6) Dolman, C. E.: Canad. J. Pub. Health, 1943, *34*:205.
(7) Barber, M. A.: Philippine J. Sc., 1914, *9*:515.
(8) Dack, G. M., Jordan, E. O., and Woolpert, O.: J. Prev. Med., 1931, *5*:151.
(9) Woolpert, O., and Dack, G. M.: J. Infect. Dis., 1933, *52*:6.
(10) Dolman, C. E., Wilson, R. J., and Cockcroft, W. H.: Canad. Pub. Health J., 1936, *27*:489.
(11) Dolman, C. E., and Wilson, R. J.: J. Immunol., 1938, *35*:13.
(12) Minett, F. C.: J. Hyg., 1938, *38*:623.
(13) Davison, E., Dack, G. M., and Cary, W. E.: J. Infect. Dis., 1938, *62*:219.
(14) Weed, L. A., Michael, A. C., and Harger, R. N.: Am. J. Pub. Health, 1943, *33*:1314.
(15) Hammon, W. M.: Am. J. Pub. Health, 1941, *31*:1191.

Records and Statistics in Venereal-Disease Control

A. HARDISTY SELLERS, B.A., M.D., D.P.H.
*Wing Commander, Royal Canadian Air Force**
Ottawa, Ontario

WE have not yet succeeded in achieving an accurate index of the extent of the venereal-disease problem. We have no idea at all of its incidence, its prevalence is a mystery, and its mortality a pure guess. It is possible that our many statistical guesses may have been near the mark. But it is more likely that they were far from the truth.

In common with advances in other fields of scientific endeavour, there have been noteworthy advances in records and statistics. These advances have involved the scrapping of traditional but cumbersome, inflexible practices in favour of adaptable recording and statistical techniques. In modern public-health practice it is recognized that adequate records and accurate statistics form essential framework for any successful program.

The maintenance of records and the preparation of reports on clinic activity and the volume of treatments carried out are useful, possibly even important, as a basis for calculating costs, estimating grants, and measuring work done, but to public health such pursuits are of minor interest. What must be provided are records which meet clinical and epidemiological needs, and statistics which serve as useful indices of control and as bases for action.

A fundamental administrative necessity in any communicable-disease control program is a uniform system whereby accurate data on the incidence and prevalence of disease may be collected, analysed, interpreted, and disseminated. Only in this way can the effectiveness of the control measures be satisfactorily assessed. So too, the success of any program for venereal-disease control is largely dependent upon the establishment of an adequate record system, with uniformity in collecting and reporting information on morbidity, treatment progress, and the general phases of control.

In order to serve the objectives, we need a uniform, comprehensive and complete notification system, a well-developed and accurate case-record organization, and an effective system of follow-up recording.

All basic records should, in the first instance, be simple. No information should be sought unless it is going to be used. Forms should be few in number and complete in content. Record and report forms required comprise a notification-of-infection form, a case record, epidemiological report forms, a form for

Presented at the National Venereal-Disease Control Conference, held in Ottawa on December 6-10, 1943, under the auspices of the Department of Pensions and National Health.
In preparing this article, material has been drawn freely from the venereal-disease control publications of the United States Public Health Service (1).
**Statistician, Medical Branch.*

notification of lapse of treatment, progress and laboratory reports, and possibly an individual or personal treatment book or card. These, together with regular statistical reports based on notifications, treatment results and clinic activity generally, complete the list.

Requirements of Medical Records from the Viewpoint of Statistical Medicine

Many investigators have given extensive consideration to the criteria of ideal clinical records. In setting up such criteria the requirements of statistical medicine, as well as those of the clinician, must be taken into consideration. As a minimum requirement, a case record should be individualistic and personal (with proper sequence), facilitate notation, yield information readily, be accurate, legible, sufficiently elastic to meet all demands, and complete (2).

The physician demands all seven of these items of his ideal clinical record, but his interpretation of completeness is frequently limited to positive information. Statistical medicine is concerned particularly with the last five requirements, the individual and personal features not being essential. It should be quite obvious that statistical research in the clinical field requires that the criteria of completeness defined by both physician and statistician should be interpreted literally and applied rigidly.

There is no reason why statistical notations should amplify the labour of recording medical data. Indeed, such procedure can minimize clerical effort. There can be no objection to tabulating medical facts in an orderly and complete fashion if in so doing both the needs of the patient and the needs of medical progress are better served. Usually the statistician is expected to pick out his own data for analysis, but all too frequently medical facts are not tabulated in a manner suitable for statistical purposes. In setting up the basic records for a venereal-disease control program, the questions should be carefully formulated to ensure that the answers will supply the required data.

Notification of Cases

An efficient notification scheme is of first importance. The notification-of-infection form must be simple, uniform throughout the area to be covered by the control plan, and limited to the essential facts on which action is going to be taken or of which use, other than academic, is going to be made. The form should be made readily available to all physicians and be transmitted in sealed envelopes, preferably to a central authority other than the local health department.

The venereal-disease notification form should be expanded beyond the form usually employed for other communicable diseases by the addition of data concerning the alleged source of infection and the facilitation process by which the individual became infected. The minimum facts are date of report, name, address, date of birth, sex, marital status and diagnosis. Minimum contact and facilitation data include name and address of contact, description, occupation and place of employment, as well as place of meeting and place of exposure. All reports should be signed and dated by the reporting physician.

Such a notification system affords valuable statistical data on incidence, sources of infection and the facilitation process. Statistics on incidence—the critical measure of the problem—can be prepared by age, sex and area, and trends established. Crucial facts on sources and modes of transmission of infection can also be determined. Reports of contacts permit the health officer to function in case-finding when the treating agency, for one reason or another, is inadequate for the situation. They also enable him to estimate, roughly, the case-finding efficiency of the treating agencies. Detailed epidemiological data must be derived from supplementary studies of groups of cases.

Clinical Records

The basic record in venereal-disease control is the individual case record. Any data subsequently prepared, any studies made or statistics compiled, depend upon the validity of the original records and errors in compilation. Clinic (case) records should provide for recording the patient's medical history, the results of an adequate physical examination, the results of laboratory and progress examinations, treatments given, reaction to treatment and tests of cure. Also, the condition of the patient at the time of any interruption in his connection with the clinic—whether because of cure, no further need for treatment, transfer for treatment elsewhere or unauthorized discontinuance of treatment—should be recorded. The identity of all of the patient's contacts and the result of their follow-up should also be noted.

Case-Holding Records

Effective case-holding record equipment is essential. For provincial bureaux or large clinics the mechanical system should be employed; for others, a manual system has been devised which is satisfactory. Both systems depend upon having accurate diagnosis and arrangements for accurate and adequate progress data. The mechanical system has a tremendous advantage in that it permits the tabulation and analysis of a large mass of data quickly and economically.

Under any system of case control, the clinic, hospital or physician concerned must provide the health department or central bureau with a notification of the case, followed by progress reports on treatment and cure, as well as reports on interruption, lapse or cessation of treatment.

Epidemiological Records

The collecting of epidemiological data begins when the health department receives the notification form of a new case. In addition, special epidemiological records are desirable. As soon as a patient's contacts are identified, an epidemiological record should be opened. After the necessary investigations have been made, the completed form should be filed as a permanent clinic record. These reports should be kept in a separate file, but the findings of the investigation should also be entered on the patient's record. In this way subsequent action and analysis are facilitated.

Lapse of Treatment

A report on premature discontinuance of treatment is not required if the mechanical system of case-holding records is employed, since lapses in treatment will be recorded in the routine progress reports made to the central bureau. When the mechanical system is not used, a notice of premature discontinuance of treatment will be required. It should provide the following information as a minimum: date of report, name and address of patient, age, sex, and marital status, diagnosis and date of diagnosis, and signature and address of reporting source.

Reports of premature discontinuance of treatment serve a dual purpose. They enable the clinic or physician to call for the assistance of the health officer in case-control, and they also make it possible for the health officer to estimate the case-holding ability of treating agencies.

In preparing the forms mentioned thus far, and in seeking data, care should be taken to ensure that the facts requested will be supplied accurately, uniformly, and regularly; that they will not annoy or seriously inconvenience the physician or alarm the patient, and that they will supply useful information.

A single form providing space for reports on morbidity, premature discontinuance of treatment, and epidemiology has been recommended. Such a scheme is advantageous in that it makes the issuance of more than one form unnecessary —the single form being used for any or all of the three purposes.

Laboratory Report Forms

Laboratory report forms should be provided by the State and should uniformly contain as a minimum, date of collection of specimen, identification of patient, identification of reporting source, reason for submitting specimen, purpose of test, and result of test.

The practice of cross-checking laboratory reports against morbidity reports has been used to assess the completeness of morbidity reporting. This is dangerous practice since very often it results in attempts to integrate two sets of data which are not of the same quality or meaning. Laboratory reports should not be considered as case reports. They are of assistance in making a diagnosis, but the diagnosis itself must be made by the physician.

It is generally agreed that "all laboratories should be required to use the terms 'positive', 'negative', and 'doubtful' in reporting the results of serodiagnostic tests"; and that all report forms should include a "statement to the effect that a single positive test, in the absence of a history or clinical evidence of syphilis, must not be accepted as final; and that a single negative test, in the presence of a history or clinical evidence of syphilis, must not be accepted as indicating freedom from infection" (1).

Nomenclature and Terminology in Venereal-Disease Recording

The nomenclature and nosology to be adopted in venereal-disease records and statistics must be agreed upon and clearly defined at the outset. The

classification recommended by the United States Public Health Service meets the need:

Chancroid.
Gonorrhoea (all forms).
Syphilis—Prenatal (Congenital).
Syphilis—Acquired—Primary.
Syphilis—Acquired—Secondary.
Syphilis—Acquired—Latent (including tentative).
Syphilis—Acquired—Tertiary—Cardiovascular.
Syphilis—Acquired—Tertiary—Other.
Syphilis—Type undetermined.

Clear definition of terms descriptive of cases is also requisite. Unless the meaning of such simple terms as "new case", "recurrence", "patient under treatment" and "cure" has been clearly set down, statistical data thereon will be confusing and therefore have limited significance. These are problems for the clinician and the epidemiologist rather than for the statistician. But the clinician, epidemiologist and statistician must plan and work hand in hand. This sort of liaison should be extended beyond the initial stages of organization into the routine day-to-day problems and in the undertaking of special surveys.

Organization—Personnel

For efficient operation, the venereal-disease control organization must include a central bureau or clearing-house to service the records and to prepare and issue statistics. Too much emphasis cannot be laid on the importance of having properly trained personnel in adequate numbers to handle records and statistics. All too often a system breaks down because of insufficient or inadequately trained staff. There is general appreciation now of the usefulness of records and a pressing demand for figures. There is all too little appreciation, however, of the fact that, while modern methods and mechanical tabulation make it possible to produce data hitherto unavailable, they do not eliminate the need for trained people to handle those records and think for the machines. It is to be hoped that the peacetime conditions, which found most public-health record and statistical departments woefully understaffed, will not be repeated. The record librarian, record clerk and statistician are now rightly regarded as occupying an important place in the administrative machinery of public health since it is through the efforts of this group that the great bulk of the material for the guidance of policy must be secured.

Venereal-Disease Statistics

Statistics are defined as facts represented by figures. They are a useful but potentially dangerous public-health tool. Improperly used, they can cause much mischief. Properly collected, analysed, interpreted and presented, they can be a potent driving force in a venereal-disease control program. They can be employed to great advantage in educational work and in maintaining the active interest of both the public and the medical profession.

Statistics on venereal disease must be complete, accurate, timely and readily available. Completeness is the first objective. Accuracy involves the education of physicians and record personnel, together with constant vigilant checking. Analyses of the data derived from morbidity reports and clinic records should be made and published at regular intervals, ***in simple form,*** for the information of the public but more especially ***for the information of medical agencies making***

the reports. Statistics should be released to the profession regularly, if possible through medical journals. Such action will go further than any amount of discussion in maintaining interest and encouraging complete reporting. The limitations of all statistical data released should be clearly stated.

It is fundamental that care should be taken to ensure that no records and reports are asked for unless use will be made of them and the product of the reports subsequently made available to those who did the reporting. In no circumstances should data be asked routinely of physicians when the information can be secured in other ways, such as by sampling or spot surveys.

Sources and Types of Statistical Data

The main sources of statistical data are notification reports, laboratory reports, hospital data, clinic records, mortality records and special surveys. All these sources are of value—but only in so far as the limitations of the data derived are recognized and the facts are carefully interpreted. For example, in 125,000 routine serological tests carried out on male Air Force personnel after enlistment, 3.5 per 1,000 were found to be positive. This statistic is interesting and useful but it throws no light whatever upon the prevalence of syphilis in the population as a whole or even in males of comparable ages.

Statistical data which should be made regularly available include:

(*a*) Data on cases
  i. Incidence—by disease, age, sex, area and occupation.
  ii. Prevalence—by disease, age, sex, area and occupation.

(*b*) Data on sources and modes of infection including
  i. Place of exposure.
  ii. Age of contact.
  iii. Facilitation process.

(*c*) Data on treatment and follow-up results
  i. Cures, cure rates.
  ii. Relapses, recurrences.
  iii. Methods of treatment.
  iv. Follow-up.
  v. Lapse of treatment.

(*d*) Special surveys—mass serological testing, etc.

(*e*) Clinic performance—cases treated, treatments given, etc.

Statistics based on notification reports should be released not less frequently than once a month. In such reports, the case incidence (reported new cases) should be expressed in terms of cases per 1,000 population per annum. Tabulations should be made separately for each disease and for all diseases combined, together with appropriate breakdowns by age, sex and area. The same practice should be followed in reporting upon the prevalence of venereal diseases (number of cases in the population at any one time). In all statistical reports the greatest care should be taken to distinguish clearly between statistics on incidence and those on prevalence.

An annual report should also be made and should include data on all the foregoing facts together with an analysis and interpretation of them. Trends should be discussed and epidemiological facts reviewed. Information by sex, age and area should be included in all annual reports but extreme caution should be used in the interpretation and presentation of all rates. There are many variables in both the numerator and denominator of all such ratios.

Analysis of Morbidity Data

The primary objective for requiring the reporting of venereal disease is to enable the public-health authorities to measure the extent of the problem, to discover the sources of infection and to control the spread of disease. Analysis of notification reports should therefore be provided for either through the mechanical system or some simpler punching and sorting system.

The objective of ordinary analysis of morbidity reports is to ascertain:

(*a*) The relation of the disease to sex, age, marital status, etc.

(*b*) The ratio of fresh infections to total infections in all stages by sex, age and marital status.

(*c*) The extent of movement of patients from their community of residence to other centres for treatment.

(*d*) The variation in case-reporting in different areas and the relation of such variation to population differences, availability of clinics and other treatment services, and the co-operation of the medical profession.

In provincial venereal-disease control departments, an epidemiologist should be employed to direct the collection and analysis of morbidity data, to make special studies, and to prepare material for publication. The assistance of a trained statistician should be sought to direct the preparation of statistical analyses.

Limitations of Morbidity Data

Like other communicable-disease statistics, those for venereal disease are subject to error of which the most serious is incomplete reporting. Comparability even in time and place is, at the moment, just as mythical in the case of communicable-disease statistics as in cause-of-death statistics. As long as their limitations are kept in mind, no serious harm should result.

Since only a fraction of the new cases may come under treatment early, and since reporting is very incomplete, ***notification reports should be used only as a partial indication of the incidence and prevalence of venereal disease.*** They must be used with caution even to estimate the distribution of infection in the population according to age, sex or marital status, or as any measure of the proportion of fresh infections to total infections among persons seeking treatment. ***They should never be depended upon entirely to measure the extent of the problem in the population.*** Special surveys of representative groups of the population in the area under consideration must be conducted for this purpose. When population sampling is undertaken, the utmost care should be exercised and expert technical advice secured before any special survey is launched.

Great caution should also be exercised in using morbidity data even as an indicator of trends in venereal-disease incidence. There are many factors, apart entirely from actual changes in the incidence of infection, which may account for observed fluctuations in the number of cases reported. Among such factors are the availability and accessibility of treatment facilities, the interest of physicians, the public interest in and understanding of venereal diseases, and changes in the concentration or composition of the population.

Mortality Records and Statistics

Official statistics on causes of death are essentially useless as an index to most health problems. More than that, in a great many cases they are actually misleading. At most the only reliable facts which we can get from cause-of-death tables are total deaths, some communicable diseases and accidents. In the case of venereal disease, no amount of juggling of mortality figures will produce any data which deserve the name of statistics or which are of even the slightest value in control. This is no reflection on the physician. Because an individual has had syphilis, or because he had a positive Wassermann test at the time of death, is no reason for anyone to assume that he died from it (3). The solution does not lie in confidential certification of deaths.

Special Studies

Epidemiological data and information on the part played by alcohol, the value of prophylaxis, etc., in venereal diseases should be secured by special studies. Addition of such facts on routine notification reports serves no useful purpose except in the armed forces, where it is sometimes easier to secure complete recording.

Special studies of certain population groups should also be made as an aid in determining the proportion of the population infected with venereal disease. Such studies made at given intervals may prove helpful in establishing possible trends and in pointing out special needs for the control of venereal disease in specific population groups or areas. Studies might include inmates of mental and penal institutions, workers in industry, admissions to public hospitals, and patients in prenatal clinics. In studying selected population groups, it is highly important to employ proper statistical safeguards, especially with reference to the age and sex composition of the group. The limit to which results of studies on selected population groups can be applied to the total problem must be recognized, inasmuch as selected population groups are rarely mutually exclusive or representative samples of the whole population.

In view of the desire for national agreement, uniformity and standardization in venereal-disease control efforts and particularly in relevant record and statistical practices, I cannot do better than quote the words of Dr. Haven Emerson (4):

> "Consistency, uniformity, standardization are all qualities of official performance which may either create a false sense of excellence, while in fact expressing no more than a dull and lifeless habit or routine repetition of traditional methods, or may express the co-operative competence of a body of officers of government all equally alert to the necessity of constant adjustments of the authority of the law and the force of public education to the development of new knowledge, and prepared by their professional organizations to use the democratic methods of open discussion and representative committee work to keep their public services abreast of the facts."

REFERENCES

(1) Supplement No. 17 to Venereal Disease Information, United States Public Health Service, 1943.
(2) Dunn, H. L., J.A.M.A., 1927, *89*: 1273.
(3) Sellers, A. H., Am. J. Pub. Health, 1938, *28*: 430.
(4) Emerson, H., Am. J. Pub. Health, 1942, *32*: 136.

Influenza in Canada during the Autumn of 1943

JAMES W. FISHER AND PEARL SCOTT
Department of Hygiene and Preventive Medicine
and
Connaught Laboratories
University of Toronto

THERE is some evidence that influenza A tends to occur at two-year intervals. In England influenza A virus was isolated in 1933 (1), 1935 (2), 1937 (3), early 1939 (4) and early 1941 (5), while in North America outbreaks occurred in late 1934 (6, 7), early 1937 (8, 9), early 1939 (9, 10) and late 1940 (11, 12). If a period of two years elapses between such epidemics, a fifth epidemic should have appeared in late 1942 or early 1943. An epidemic did occur, but there is no evidence that the causative virus was influenza A. It is more probable that it was influenza B. In England about 44 per cent of the cases of influenza from the middle of December, 1942, to the middle of February, 1943, gave serological evidence of infection with type B virus (13); one strain of this virus was isolated (14). In North America the epidemic appeared later. At present, there is no published information for the United States other than statistical reports; but the outbreak of influenza B in Canada, occurring in Ontario in February and in Alberta and British Columbia in March, has been described (15).

It appears, therefore, that there were outbreaks of influenza B on both sides of the Atlantic ocean in the winter of 1942 and 1943. At this time influenza A failed to occur to any significant extent. However, a few cases were encountered, 1.8 per cent in Canada (16) and 2.5 per cent in England (13), in which there was an increase in titre to influenza A virus. It is debatable whether such increases in titre to this virus during a B epidemic are to be considered valid evidence of an influenza A infection. It seems unlikely that these increases are due to an antigen common to influenza A and B viruses (17, 18, 19, 20). On the other hand, they might be attributed to a bacterial contaminant in the acute-phase sera (21). The true explanation must await future research. All that can be said at present is that influenza A was not common during the period in question, whereas influenza B was.

Following these epidemics, in Canada at least and probably elsewhere as well, there was in general a period in which the incidence of influenzal-like infections was low. Nevertheless, during this interval small, circumscribed epidemics occurred in both England and North America. Stuart-Harris and Glover (13), having examined sera from localized outbreaks in East Anglia in March and May, concluded that they were probably due to influenza A since about 36 and 57 per cent of the cases, respectively, gave a significant rise in titre for that virus and not influenza B. Another localized outbreak occurred in Scotland, and again similar rises in antibody levels to influenza A virus were observed. In North America events of a similar nature took place. Salk et al (22) actually isolated influenza A virus from one of several patients in Michigan

who were ill with influenza on May 28th, while two other cases gave serological evidence of an influenza A infection. In Canada, Hare et al (16) described a localized epidemic in April in which nine out of twelve cases in a hospital situated in the midst of a large military camp were probably of influenza A.

Investigations have shown, therefore, that at a time when influenza A was expected, influenza B actually occurred. Nevertheless, influenza A was not far distant because during the subsequent period there were small, circumscribed outbreaks of this infection. It is of interest to note that these events happened almost simultaneously in England and Canada.

During the summer of 1943 there was no abnormal amount of upper respiratory-tract infection, but in November it became evident that there was an increase in the incidence of these infections in both England and North America. Reports from England indicate that an influenza epidemic began in that country probably

RESULTS OF SEROLOGICAL TESTS ON PAIRS OF SERA FROM CASES OF CLINICAL INFLUENZA, AUTUMN, 1943

Place	Date when first serum specimen was obtained	Date when second serum specimen was obtained	Number of paired specimens	Increase in titre to					
				Influenza A			Influenza B		
				Fourfold or greater	Two or threefold	Less than twofold	Fourfold or greater	Two or threefold	Less than twofold
ALBERTA:									
Edmonton (Air Force)	Nov. 18	Dec. 12	9	9	0	0	0	2	7
ONTARIO:									
Camp Borden (Army)	Dec. 5	Dec. 16	6	4	1	1	0	1	5
Toronto (Navy)	Nov. 17	Dec. 10	7	5	2	0	0	0	7
Toronto (Civilian)	Nov. 17	Dec. 16	1	1	0	0	0	0	1
	Dec. 10	Dec. 18	1	1	0	0	0	0	1
	Dec. 11	Dec. 24	1	1	0	0	0	0	1
	Dec. 20	Jan. 3	1	0	0	1	0	0	1
	Dec. 28	Jan. 1	1	0	0	1	0	0	1

between November 13th and 20th, reached its peak in the week of December 4th to 11th, and then abruptly subsided (23). In the United States the number of cases of influenza reported from November 20th to 27th was greater than that of the preceding week, and thereafter the incidence of influenza increased until the peak was reached during the first week of January. By the middle of February the epidemic had almost disappeared (24). In Canada, the epidemic occurred at about the same time as the one in the United States, and in places as widely separated as Nova Scotia, Ontario, Alberta and British Columbia. The peak level for the country as a whole was in the week of December 25th to January 1st. By February 12th the epidemic was over (24).

In the United States, the Commission on Influenza (25) had set up a number of observation posts in various parts of the country. It was reported

by Salk et al (22) that influenza A was present in Michigan on November 17th and 18th, the virus being actually isolated. In the middle-western states of Minnesota and Iowa epidemic influenza occurred on November 21st and 29th respectively, and in California on November 26th. In the East it was observed in New Jersey at two posts on November 22nd and 28th, and in New York at one post on November 7th and at two other posts on November 23rd. The diagnosis of these cases, called influenza, was made without reference to serological or other methods for identification of the aetiological agent. However, Thigpen and Crowley (26) at Minnesota later reported that influenza A virus had been isolated from material obtained during the epidemic.

This paper presents observations on illnesses clinically diagnosed as influenza in Canada during the same period. From Edmonton, Alberta, we obtained nine specimens of sera taken on November 18th during the early stages of infection, and from Ontario eighteen specimens taken between November 17th and December 28th. A second sample was obtained from ten days to a month later. The paired sera were examined serologically by the agglutination-inhibition method (27, 28). The results of the tests are presented in the table. All nine specimens from Edmonton showed a fourfold or greater increase in antibody to influenza A, and none to influenza B. Of the eighteen specimens from Ontario, 12 showed a similar significant increase to influenza A but not to influenza B; 6 of these positive sera were obtained on November 17th.

There is good reason for believing, therefore, that influenza A was present in Ontario and Alberta on November 17th and 18th. From the report of Salk et al (22) it appears that influenza A was also present in Michigan on those dates. Unfortunately we do not know the date when influenza A was first detected in England; but as epidemiological reports indicate that influenza was definitely on the increase in the week of November 13th to 20th, and since preliminary tests have shown that influenza A was the predominant type of infection (13), it is highly probable that an epidemic of influenza A was also in its early stages in England on or about November 17th or 18th. It should be emphasized that on these dates, when influenza A was first detected in Alberta, Ontario and Michigan, the incidence of influenza was not great. In these places the epidemic was just starting and the peak period came much later.

The investigations just described show that influenza A virus may appear in different parts of the world during inter-epidemic periods and cause small, circumscribed outbreaks which have little tendency to spread. It is possible, however, that during this period a "seeding" of the population occurred with a strain of influenza virus which remained latent. Subsequently a suitable provocative stimulus may have reawakened the virus, with the production of clinical cases. In this respect the pattern of the human infection would simulate that of swine influenza described by Shope (29). In the present instance, this stimulus apparently acted at about the same time in North America and England, so that influenza began more or less simultaneously in areas geographically far apart. The alternative hypothesis, that case-to-case transmission occurred from one or more foci, fails to harmonize with the observations presented here.

Summary

An outbreak of influenza A in various centres of Canada during November and December, 1943, is reported.

There is serological evidence that about 78 per cent of the cases were due to infection with influenza A virus.

Acknowledgments

We are indebted to Squadron Leader G. O. Prieur, R.C.A.F., and Dr. R. M. Shaw of the Provincial Laboratory, Alberta, for the specimens of sera from Edmonton; to Major W. R. Feasby, R.C.A.M.C., for the specimens from Camp Borden; to Surgeon Lieutenant Rice, R.C.N.V.R., for the specimens from a naval training station at Toronto; and to the personnel of these laboratories for their co-operation. We wish to express appreciation to Dr. A. Somerville, Director of the Division of Communicable Diseases, Province of Alberta, for providing information regarding the incidence of influenza in a command of the R.C.A.F. in Alberta. We desire also to thank Dr. Ronald Hare for much assistance and advice.

REFERENCES

(1) Smith, W., Andrewes, C. H., and Laidlaw, P. P.: Lancet, 1933, *225*: 66.
(2) Laidlaw, P. P.: Lancet, 1935, *228*: 1118.
(3) Hoyle, L., and Fairbrother, R. W.: Brit. M.J., 1937, *i*: 655.
(4) Stuart-Harris, C. H., Smith, W., and Andrewes, C. H.: Lancet, 1940, *238*: 205.
(5) Andrewes, C. H., Glover, R. E., Hudson, N. P., Lush, D., and Stuart-Harris, C. H.: Lancet, 1941, *241*: 387.
(6) Francis, T., Jr.: Science, 1934, *80*: 457.
(7) Francis, T., Jr.: Proc. Soc. Exper. Biol. & Med., 1935, *32*: 1172.
(8) Francis, T., Jr., Magill, T. P., Beck, M. P., and Rickard, E. R.: J.A.M.A., 1937, *109*: 566.
(9) Hare, R., and Rheim, W.: J. Immunol., 1941, *40*: 253.
(10) Horsfall, F. L., Jr., Hahn, R. G., and Rickard, E. R.: J. Clin. Invest., 1940, *19*: 379.
(11) Hare, R., Auger, W. J., and McClelland, L.: Canad. Pub. Health J., 1942, *33*: 72.
(12) Lennette, E. H., Rickard, E. R., Hirst, G. K., and Horsfall, F. L., Jr.: U.S. Pub. Health Rep., 1941, *56*: 1777.
(13) Stuart-Harris, C. H., and Glover, R. E.: Lancet, 1943, *245*: 790.
(14) Himmelweit, F.: Lancet, 1943, *245*: 793.
(15) Hare, R., Stamatis, D. M., and Jackson, J.: Canad. J. Pub. Health, 1943, *34*: 442.
(16) Hare, R., Hamilton, J., and Feasby, W. R.: Canad. J. Pub. Health, 1943, *34*: 453.
(17) Francis, T., Jr.: Science, 1940, *92*: 405.
(18) Gordon, I.: J. Immunol., 1942, *44*: 231.
(19) Foley, M., and Burnet, F. M.: Med. J. Australia, 1941, *28*: 468.
(20) Friedewald, W. F.: J. Exper. Med., 1944, *79*: 633.
(21) Bodily, H. L., and Eaton, M. D.: J. Immunol., 1942, *45*: 193.
(22) Salk, J. E., Menke, W. J., and Francis, T., Jr.: J.A.M.A., 1943, *124*: 93.
(23) Epidemiological Notes, Brit. M.J., 1944, *i*: 101.
(24) Dominion of Canada Bureau of Statistics, Weekly Reports, as reported by the Provincial Health Departments, 1943.
(25) Members of the Commission on Influenza: J.A.M.A., 1944, *124*: 982.
(26) Thigpen, M., and Crowley, J.: Science, 1943, *98*: 516.
(27) Hirst, G. K.: J. Exper. Med., 1942, *75*: 49.
(28) Hare, R., Morgan, J., Jackson, J., and Stamatis, D. M.: Canad. J. Pub. Health, 1943, *34*: 353.
(29) Shope, R. E., in Virus Diseases, Cornell University Press, Ithaca, N.Y., 1943, p. 83.

An Epizootic of Influenza A in a Ferret Colony

JAMES W. FISHER AND PEARL SCOTT
Department of Hygiene and Preventive Medicine
and
Connaught Laboratories
University of Toronto

FEW if any epizootics of influenza due to a human strain of virus occurring in a colony of uninoculated ferrets have been described, although Francis and Magill (1) and Burnet and Lush (2) encountered apparently normal ferrets which were resistant to experimental infection with influenza virus. These animals came from breeders' stocks and their history is unknown. Shope (3), however, observed swine that possessed influenza A neutralizing antibodies and concluded that these animals had probably been previously infected following the consumption of garbage contaminated with human virus. McBryde et al (4) discovered swine which were resistant to swine influenza, probably as a result of contact with the disease prior to their use experimentally; and Shope (5) obtained, from a breeder, swine which possessed a low titre of neutralizing antibodies for swine influenza virus. This paper reports an epizootic of influenza which occurred in a ferret colony at a time when influenza was epidemic in the human population.

The ferrets are all housed and bred under good conditions at the farm section of the Connaught Laboratories in the open country well away from centres of human habitation. The animals are housed in one room $18' \times 18' \times 7'$ in which there are two rows of cages placed back to back, each row consisting of twenty-four cages distributed in four tiers. Four ferrets are kept in one cage. They are attended by one man with the assistance of one girl. The feeding and handling of the ferrets, as well as cleaning of cages and trays, are done by the man, while the feed bowls are washed by the girl.

Up to the time of the outbreak, the ferrets had been remarkably free from any known infection. The colony was established in 1937 and had passed through epidemics of influenza A in 1939 (Hare and Rhiem, 6) and 1940 (Hare et al, 7), as well as an epidemic of influenza B in 1943 (Hare et al, 8) without any clinical or serological signs of infection. When material from human cases who had had influenza A in November and December, 1943 (Fisher and Scott, 9), was ready to be studied, serological tests were carried out on sera from a random sample of the ferrets in order to determine their susceptibility to influenza A. It was observed that the sera of all the ferrets tested possessed a high titre of agglutinin inhibitory antibodies. Upon enquiry it was learned that the ferrets in the farm colony had suffered a mild upper respiratory-tract infection during the time influenza was epidemic in this province.

In Ontario an epidemic of influenza began in the week of November 20th to 27th; the peak period was reached during the last week of January, after which the number of cases sharplv abated to their normal proportions by about

February 12th (10). On the other hand, in the ferret colony, influenza first appeared on December 15th, reached its peak at the end of January and had disappeared by February 1st. On December 15th several ferrets in the upper cages situated near the door leading to the open air began sneezing. The following day the male attendant observed that they had a mild coryza accompanied by anorexia and for this reason they were removed to other isolated quarters. In spite of this, however, the epizootic spread throughout the colony so that by January 31st over 95 per cent of the 156 ferrets had been infected. Two animals died, one on December 31st and the other on January 28th, with marked rhinorrhoea. Post-mortem reports made no mention of pulmonary involvement. Unfortunately no material was made available for future study.

As far as we have been able to ascertain, neither of the attendants while actually suffering from an upper respiratory-tract infection had contact with the ferrets. However, the male attendant was absent from work from November 30th to December 4th with a mild "cold" accompanied by chills and a slight fever. It was not until eleven days after his return that the ferrets manifested signs of disease. Serological examination of serum from this individual taken early in April showed an agglutinin inhibitory titre of 1 in 728 for influenza A virus (PR-8) and 1 in 32 for B virus (Lee).

Twelve per cent of the ferrets chosen from representative cages in the room were removed to the city laboratory on February 16th and placed in isolation. The following day they were bled by cardiac puncture. They were all infected on February 21st by the intranasal instillation of 2 ml. of a suspension of the lungs of mice which were killed forty-eight hours after receiving intranasally a potent strain of influenza A virus (PR-8), which had recently been submitted to six unbroken serial passages in mice. The dose consisted of 20×10^4 m.l.d. for mice.

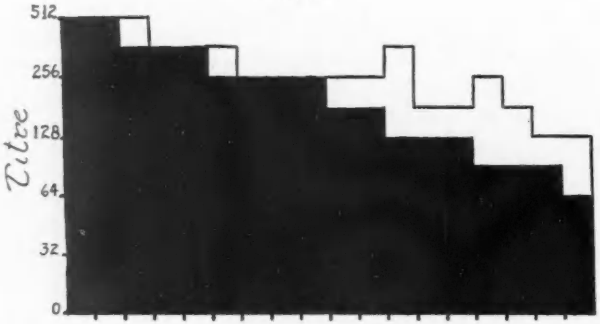
Records were kept of the temperatures and clinical conditions of the animals. The highest temperature recorded was 104.6°F., the arithmetic mean being 103.8°F., and none of the ferrets manifested signs suggestive of clinical influenza. On March 2nd, the animals were bled a second time. The two specimens of sera from each animal were inactivated at 37°C. for half an hour and were simultaneously tested for their ability to inhibit the agglutination of fowl erythrocytes in the presence of allantoic fluid containing either influenza A (PR-8) or B (Lee) viruses by the method of Hirst (11) as modified by Hare et al (8) and need not be described.

All of the ferrets possessed an initial level of influenza B antibodies below a titre of 1 in 24 which failed to increase following the experimental infection. The results obtained on testing for influenza A antibodies are presented in the figure on page 366, from which it will be observed that intranasal instillation of virus produced little change in the already high antibody level. The maximum increase in titre was two and a half times.

On the basis of this evidence, there seems to be little doubt that the ferrets had had an infection with influenza A virus on December 15, 1943. Although there is no direct causal relationship between the outbreak in the colony and any

human case, other than the one mentioned on page 365, it should be noted that December 11th to 18th was one of the peak periods of the autumn influenza epidemic in Ontario (10), and that December 13th was the peak for the number of reported cases in Toronto (12). Accordingly, at the time the ferrets first showed signs of infection there was a large number of influenza cases in the human

FIGURE I



Titres before and after experimental infection with type A influenza virus. Solid and open columns, respectively, give the titres before and after instillation of virus.

population. The evidence given for the diagnosis of this infection is, however, only circumstantial, since virus was not isolated. Nevertheless, it may be assumed that failure to obtain evidence of clinical influenza after intranasal instillation of a potent dose of influenza A virus in ferrets which had had an upper respiratory-tract infection a month previously, and which possessed a high level of influenza A antibodies, is strong presumptive evidence of a previous natural infection with influenza A virus.

SUMMARY

An epizootic of influenza which occurred in an isolated colony of uninoculated ferrets is reported.

Serological and immunological evidence indicate that the aetiological agent was influenza A virus.

The source of the infection was probably the man who attended the ferrets.

REFERENCES

(1) Francis, T., Jr., and Magill, T. P.: J. Exper. Med., 1935, *62*: 505.
(2) Burnet, F. M., and Lush, D.: Australian J. Exper. Biol. & Med. Sci., 1940, *18*: 49.
(3) Shope, E. R.: J. Exper. Med., 1938, *67*: 739.
(4) McBryde, C. N., Niles, W. B., and Moskey, H. E.: J. Am. Vet. A., 1928, *73*: 331.
(5) Shope, E. R.: J. Exper. Med., 1941, *74*: 49.
(6) Hare, R., and Rhiem, W. C.: J. Immunol., 1941, *40*: 253.
(7) Hare, R., Auger, W. J., and McClelland, L.: Canad. Pub. Health J., 1942, *33*: 72.
(8) Hare, R., Stamatis, D. M., and Jackson, J.: Canad. J. Pub. Health, 1943, *34*: 442.
(9) Fisher, J. W., and Scott, P.: Canad. J. Pub. Health, 1944, *35*: 360.
(10) Dominion of Canada Bureau of Statistics, Weekly Reports, as reported by Provincial Health Departments.
(11) Hirst, G. K.: J. Exper. Med., 1942, *75*: 49.
(12) Daily Report of Communicable Diseases, Department of Public Health, City of Toronto.

Canadian Journal of Public Health

EDITORIAL BOARD

R. D. DEFRIES, M.D., D.P.H., *Editor*
N. E. MCKINNON, M.B., AND J. T. PHAIR, M.B., D.P.H., *Associate Editors*
R. L. RANDALL, *Assistant Editor*

A. MARGUERITE ARCHIBALD, M.D., D.P.H. GORDON BATES, M.D. A. E. BERRY, M.A.SC., C.E., PH.D. J. CRAIGIE, M.B., CH.B., PH.D., D.P.H. J. G. CUNNINGHAM, B.A., M.B., D.P.H. C. E. DOLMAN, M.B., B.S., PH.D., D.P.H., M.R.C.P. D. T. FRASER, M.C., B.A., M.B., D.P.H., F.R.S.C. RONALD HARE, M.D. EDNA L. MOORE, REG.N. E. W. MCHENRY, M.A., PH.D. R. M. MACPHERSON, B.A., C.S.I.(C.). G. D. PORTER, M.B. A. H. SELLERS, B.A., M.D., D.P.H. F. O. WISHART, M.A., M.D., D.P.H. J. WYLLIE, M.A., M.D., CH.B., B.SC., D.P.H.

MILITARY REJECTIONS AND THE PUBLIC HEALTH

THE Services serve us well overseas, but they also serve us here in other ways. They have revealed, according to the latest figures given out by the Prime Minister in the House of Commons, that over one half of the prospective personnel examined by the Army in recent months were unfit for enlistment in any sphere of service. Over one half were rejected on medical grounds! Added to the defects indicated by these rejections are the numbers accepted with remedial defects—of eyes and teeth, hernias, orthopaedic conditions, etc. Added to these again are break-downs from pre-existing conditions even before the trainees reach other theatres of action. The situation thus indicated reflects very unfavourably on the state of the public health, with which the public-health and medical professions must be duly concerned.

As the state of the public health is a matter of direct provincial concern, provincial health authorities should be in possession of all available information so that remedial action may be undertaken in co-operation with the medical and dental professions. The problem both in magnitude and time is urgent.

Institution of remedial action, however, requires a much more detailed knowledge of conditions than is available in the figures as published. For instance, what are the various standards for rejection? Have they varied, and how, and with what result, in rejections and in subsequent wastage or serviceability of those accepted? Have the rejection rates been reasonably uniform throughout Canada or have they varied significantly in different areas and in different periods? What has been the relative importance of the various causes of rejection and subsequent wastage, and how have the rates for these causes varied in the different military districts? How have they varied with age, and with training environment? At the same time, what are the findings regarding the Women's Army?

As these questions are fundamental from the standpoint of national defence, it is to be hoped that the analysis suggested will be undertaken and that the answers will be made available immediately to the provincial Ministers of Health. Military secrecy is in no way involved in them. Without that full and detailed information, correction of conditions is certain to be long delayed; and, con-

sidering even tomorrow rather than today—even the possible next war rather than this one—delay is inimical to the national good.

Regrettable as it is that our contributions of manpower to the Services have shown such a high proportion of defects and rejections and have fallen so far short of the ideal, the revelation of such conditions is a distinct contribution to the public health. Now that we are aware of this state of affairs, action can be taken to correct it. And action should also be taken to ensure that, in future, our health bookkeeping is improved so as to reveal constantly the actual state of the public health. To hazard another war to reveal our deficiencies would be, to say the least, a short-sighted policy.

"GRAUNT WAS A MAN OF ONE BOOK"

"GRAUNT was a man of one book." So says Greenwood in his Fitzpatrick Lecture,[1] *From Graunt to Farr*, an outstanding analysis which should be read by all those interested in humanity's problems—including physicians, surgeons and public-health administrators as well as vital statisticians. The book was a small volume written in 1661 which has kept and will keep the name of Graunt current through the centuries.

What a castigation, it may perhaps be inferred, lies in Greenwood's short sentence, a castigation not only of the prolific writers of the past but of those of today who even in time of war, when paper as well as manpower is scarce, fill the many journals with material which will neither "alter the face of science nor excite the admiration of the ages." Why this continuous flood of immature and premature publications? Too often it is attributed to the director's policy, the demand of the departmental head. In fact, though, this is the reason for only a very small part. The fault lies more with the individual, born, through no fault of his own, with the "tang to write." That tang overcomes any inhibitions due to lack of essential knowledge. It is frequently associated with enthusiasm and ambition. If it is not an inherited trait, it is one which, given the environment, quickly develops. Some of the blame must be accepted by those who measure competency and ability by the number of publications.

It is not easy to meet the problem. Even Hippocratic anonymity would hardly serve to stem the spate of stuff, as it is not uncommon now for the ambitious enthusiast to collect his reprints, adorn them in vellum binding, gilt-inscribed, and, under the guise of gratitude, present the volume to his alma mater, or to the institution from which he has derived his sustenance—though, it is to be hoped, not his inspiration to publicize. Perhaps, if from every contributor a bond were required that the report would not be refuted in a year or two, we might obtain some relief, and a saving of paper, time and temper. But perhaps it is better to leave it for correction to evolution in the scheme of things—an easier and safer alternative.

[1]Biometrika, 1941, *32*: 101.

Books

Clinical Tropical Medicine. Edited by Z. Taylor Bercovitz, M.D., Ph.D., F.A.C.P., Assistant Clinical Professor, New York Post-Graduate Medical School, Columbia University; Physician-in-Charge, Parasitology Service, Department of Health, City of New York; Consultant in Tropical Medicine, Ellis Island Hospital, United States Public Health Service. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, 1944. 957 pages. $14.00 U.S. funds.

THIS new book on tropical medicine is planned to give the medical student a definite picture of tropical diseases, their symptomatology, pathology and the most authentic and effective therapeutic and preventive measures. In the foreword, Dr. Wilbur A. Sawyer truly says: "The value of a manual of this kind depends upon the authoritative position of the contributing scientists, and it is gratifying to find among those who have taken part in the production of this volume so many persons of broad experience and scientific distinction."

The book has been carefully prepared and the clear-cut didactic presentation makes it very suitable for students. Special attention should be called to the excellent series of plates on intestinal protozoa by Dr. C. A. Dobell, the original slides of microfilaria prepared by the late Dr. F. W. O'Connor, and the coloured plates of malaria parasites from Dr. C. M. Wenyon's Protozoology. The advantage of using thick blood films in the diagnosis of malaria is illustrated by coloured plates redrawn from those in original articles published by Field and Flemming in the Transactions of the Royal Society of Tropical Medicine and Hygiene. Coloured plates of gross specimens of the bowel in amoebic and bacillary dysentery might have been added.

Diseases already covered in standard textbooks of medicine could have been omitted, such as typhoid fever, smallpox, chickenpox, rabies, epidemic encephalitis, and poliomyelitis. Fifty-one pages are devoted to the discussion of these diseases and a further seven pages to trachoma, which the author admits is universal in its distribution.

The Diarrheal Diseases. Attention is properly called to the necessity for the correct diagnosis in cases of dysentery in the tropics, as the possible causes are more numerous there than elsewhere and proper treatment must of necessity be based upon a correct diagnosis. The reviewer agrees with the author that in the treatment of amoebiasis, Chiniofon (Yatren) is the drug of choice and that emetine hydrochloride should be employed only to control the symptoms of acute amoebic dysentery.

The chapter on *Laboratory Methods in Intestinal Protozoa* is very helpful. The details for the preparation of a medium best suited for the cultivation of *E. histolytica* might have been added.

Bacillary Dysentery. The use of only one of the sulfa drugs, sulfanilylguanidine, is mentioned in the treatment of this disease. Some of the other sulfa compounds have been shown to be more effective and are much less bulky for shipment, an important consideration in wartime.

Cholera. In this section a description of one of the new methods of determining the specific gravity of the blood as is used in "shock" might have been added. No mention is made of the efficacy of sulfa drugs. Permanganate of potash and essential oils are mentioned as methods of treatment, but is there any proof that they are of value? Some assessment as to the value of kaolin would also be helpful. Cholera is often a rapidly fatal disease with a high mortality. A doctor confronted with this disease for the first time needs to know what to do first, and what value to place upon comparative methods of treatment. The treatment of "shock" which occurs in this disease is given in detail.

Malaria. On page 180 the author states that "for the elimination of a malarial infection quinine must be administered for at least eight weeks after an attack has subsided." Although it is stated that 70 - 80 per cent of cases will relapse (authority not stated) if treated for only a short time, there is no statement regarding the percentage of relapses following the course of eight weeks. The statement that eight weeks' treatment is necessary is made rather dogmatically considering that other authorities on methods

of treating malaria prefer to treat the first attack for one week only or until the attack is relieved. Moreover, if every patient is treated for a period of eight weeks, the present need for conserving stocks of quinine may be overlooked.

There is no reference in the bibliography on malaria to the excellent articles on the treatment of malaria in the Bulletins of the Health Organization of the League of Nations.

Kala-azar. The statement on page 231 that "the parasites can not be regarded as completely exterminated until the spleen has gone back to its place within the costal margin" needs revision, since spleens in kala-azar patients who have apparently been cured may remain enlarged for years. Also it has been found that after a course of treatment has been completed parasites may be found but the patient proceeds to complete recovery without further treatment. If it is necessary to use tartar emetic in treatment (and this should be done only if pentavalent antimony compounds are not available) then it is better to begin with not more than one-quarter to one-half of a 2 per cent solution—not 2 cc. as recommended.

Plague. Sulfathiazole is mentioned as possibly of some value in treatment. There is now evidence that this drug has proved effective in the treatment of a number of plague patients.

Helminths. This is one of the best sections of the book, with adequate directions for the treatment of diseases caused by helminths.

Throughout the book treatments are up-to-date and represent the best in modern teaching. The reviewer has no hesitation in recommending this excellent book either as a text for the teaching of students or as a reference book for the busy practitioner. For one going abroad, however, the weight—five pounds—will be a consideration.

ERNEST STRUTHERS.

Food Poisoning: Its Nature, History and Causation, Measures for its Prevention and Control. By Elliot B. Dewberry. London: Leonard Hill Limited, 17 Stratford Place, W.1, 1943. 186 pages. 15 shillings.

THE war has for various reasons brought increased risks of food poisoning. The recorded incidence has been lower than might have been expected, a fact which may perhaps be attributed to the hotel and restaurant chef, the cafeteria and institutional dietitian, the camp cook and the housewife having gleaned at least some inklings of the newer knowledge of the causes and prevention of food poisoning. A quicker spread of this knowledge must await its thorough absorption by the medical health officer, the public health nurse, and the sanitary inspector, who perforce depend largely on up-to-date text-books. Although texts on the culinary art and the science of nutrition are multiplying, their authors appear to find the subject of food poisoning distasteful, and seldom allude to it. Publication of this book is therefore well-timed.

We would judge the author to be a sanitarian. He makes no claim to have done original work on food poisoning, but objectivity is hence perhaps gained, and the book represents a reliable enough account of current views on this topic. The greater part of the work is devoted to bacterial food poisoning, but there are chapters on contamination of food by poisonous metals, on poisonous plants and fish, and on food allergy. There are also appendices on the contamination of foods by poisonous gases in war, and on the steps to be taken by medical health officers when food poisoning is suspected. The latter appendix is a reproduction of a Ministry of Health circular containing some helpful suggestions respecting methods of conducting inquiries into food-poisoning outbreaks. The directions given in this circular for the identification of Salmonella types are somewhat out-of-date, and moreover give undue emphasis to the view prevailing at the Ministry of Health (at least until very recent years) that micro-organisms of the Salmonella group, and their alleged toxins, are the most frequent cause of bacterial food poisoning. No bacteriological methods are given, either in this circular or in the text at large, for the laboratory diagnosis of the far more prevalent staphylococcal food poisoning. This condition is indeed treated altogether too briefly, about three pages only being given to it, as compared with no fewer than eight chapters, or about one-quarter of the whole text, on various aspects of botulism, of which there have been only a dozen cases recorded in Great Britain, and fewer still in Canada.

Bacteriologists will note several rather

amateurish touches: for instance, staphylococcus enterotoxin is referred to as "these endotoxins"; members of the Salmonella group are designated "Bacillus enteritidis", "Bacillus aertrycke", and so on; while separate chapters on the history, symptomatology and causation of botulism are succeeded by one headed "Spores of Cl. Botulinum", and this in turn by another chapter ingenuously entitled "Botulinum". These major points of organization and emphasis, as well as the rather numerous misprints in the text, should be corrected in the second edition. The book contains several useful illustrations, and also a selection of interesting portraits of workers in the food-poisoning field. In certain instances, there is a marked disparity between the size of the portrait reproduced and the significance of the subject's contributions to knowledge. In the next edition, all portraits might fittingly be reduced to a standard small size. Despite these reservations, the book deserves a place in the public-health worker's library as a handy summary of the salient features of an important problem.

C. E. DOLMAN.

Safe Convoy. The Expectant Mother's Handbook. By William J. Carrington, A.B., M.D., F.A.C.S., Attending Gynecologist, Atlantic City Hospital, Atlantic County Hospital for Nervous and Mental Diseases, Pine Rest Hospital, Atlantic City Municipal Hospital and Atlantic Shores Hospital; Diplomate, American Board of Obstetrics and Gynecology; Former Vice-President, American Medical Association. Toronto: Longmans, Green & Co., 1944. 256 pages. $3.00.

THIS attractively bound, readable book should be of immense value to expectant mothers, particularly during these war years when there is such a serious shortage of doctors. It is pleasing to find so much useful scientific information presented in popular form, unencumbered by technical terms.

The first chapters are devoted to antepartem care, the structure and functions of the reproductive organs, and the development of the baby before birth. *The Diagnosis of Pregnancy* furnishes interesting superstitions from many countries and times, as well as modern scientific information. *The Hygiene of Pregnancy* includes much useful advice regarding clothing, travelling, rest, smoking, and so on. Considerable space is given to diet and there is a chapter on the vitamins.

Minor ailments and complications of pregnancy are discussed and many needless fears are allayed. In connection with the subject of complications, abortion and premature labour are discussed, as well as toxæmia and the part played by the kidneys during pregnancy. Diseases such as diabetes and tuberculosis, not specifically related to pregnancy, are discussed. Superstitions relating to "marking" and birthmarks are dealt with from a scientific viewpoint, and the question of prenatal syphilis is considered in some detail.

The necessary arrangements for hospitalization take up another chapter. This is followed by a description of labour and the puerperium.

The last part of the book is devoted to the care of the infant, including breast and artificial feeding, with directions for the preparation of the formula in the latter case. There is a chapter on the common diseases of the infant which discusses many of the lesser ailments such as intestinal gas, constipation, croup, teething, etc. The importance of preventive inoculations against diphtheria, vaccination against smallpox, and preventive measures for other communicable diseases is stressed. A chapter on "Fatherhood" ends the book.

A number of young mothers who have recently read this book are unanimous that every expectant mother should read it, since it answers so many of the seemingly unimportant questions that arise during pregnancy.

A. MARGUERITE ARCHIBALD.

The Year Book of General Medicine, 1943. Edited by George F. Dick, M.D., J. Burns Amberson Jr., M.D., George R. Minot, M.D., S.D., F.R.C.P., William B. Castle, M.D., S.M., M.D., William D. Stroud, M.D., and George B. Eusterman, M.D. Chicago: The Year Book Publishers Incorporated, 1943. 784 pages. $3.50 (U.S. funds).

THE 1943 Year Book of General Medicine maintains the high standards of previous editions in spite of wartime shortages and difficulties. Any interference with physical

standards, however, is more than counterbalanced by the interesting reports on military medicine which are evident in all sections of this edition. Not only are the military topics of great interest but the impact of such problems on civilian practice in the post-war days needs to be kept before the eyes of the profession generally. This is ably done, for instance, in the opening pages of the section on Infectious Diseases as well as elsewhere throughout the book.

Peacetime interests of the profession are covered in good breadth. An indication of this is readily apparent from an examination of the "medical practice quiz" of twenty questions listed on the paper cover. To single out any one topic, even as an example, is perhaps unsafe. Mention might be made, however, of the pages devoted to abstracts about the atypical or virus pneumonias as these are of timely interest and concern. One might have expected, perhaps, that more attention would have been devoted to penicillin and its therapeutic applications since its use for civilian practice appears imminent.

F. O. WISHART.

Abstracts

On the Persistence of Falsely Positive Serologic Tests for Syphilis in Non-Syphilitic Infections

THIS article is a discussion of the problem of false positives in the serology of syphilis. Positive serology without other evidence of syphilis may be due to error in laboratory technique, true false biologic positive reactions, the presence of latent syphilis or cases of recent intercurrent infection. The last is the most important cause of error and a number of cases are presented to illustrate this point. To avoid such errors the following procedures are recommended:

"1. If the patient has recently had an acute infection of any kind, repeat the Wassermann and a precipitation test in a month or, better, two. If the test is still positive, the reaction is not due to the infection and is probably indicative of syphilis.

"2. If a history of recent infection is not obtained, the patient may still be a member of the group described by O'Leary who give 'false positive reactions which fluctuate from week to week and from month to month.' Here, weekly tests if not constantly positive may reveal the patient as not syphilitic.

"3. If spinal puncture is done, its results may settle the matter, since a falsely positive spinal fluid has not as yet been reported.

"4. In doubtful cases, Kahn's verification test may be employed, although as yet its results must be interpreted with reserve.

"5. Sera that are positive with less sensitive techniques, such as the Wassermann test, but negative with more sensitive ones, such as the Kahn or Kline tests, are probably not syphilitic."

Finally, it is stressed that anti-syphilitic treatment should not be commenced where there is any doubt whatever as to the diagnosis.

Albert E. Taussig, J. Lab. & Clin. Med., 1944, 29:473.

The Epidemiology of Cancer

THE volume of cancer morbidity and mortality offers a challenge to public-health agencies. In general, attempts at control have consisted of educational efforts to encourage early diagnosis and treatment and some provision of special facilities for this. That better results might be forthcoming is apparent if the significant features regarding the occurrence of cancer in man were more widely recognized and applied to practical ends. Thus it is known that certain occupations involving specific chemical and physical agents such as tars, chromates, X-rays and many others show an excessive cancer incidence. Some of these agents, for instance ultra-violet rays, may operate apart from industry, as witness greater frequency of skin cancers in the south and in outdoor workers. Cancer is also known to be associated with the so-called precancerous lesions and with other diseases, for example cancer of the breast in women with chronic cystic mastitis, and cancer of the tongue in syphilitic males. Probably less well known is the apparent relationship of cancer to economic status. Some surveys have shown a progressive increase in cancer mortality in

each "lower" social-economic group. The factors responsible for this are not clear. Again, cancer is related to race and marital status, cancer of the breast and uterus being more common in single and married women respectively. Finally familial factors, which may be hereditary, must be considered.

Possible public-health applications exist in our present knowledge of cancer in that education may be specially directed along certain lines, and case-finding and follow-up be directed to certain groups in which the morbidity and mortality from cancer are apparently high.

Morton L. Levin, Am. J. Pub. Health, 1944, 34:611.

Food Poisoning Caused by Haemolytic Staphylococcus in a Defence Plant

THE outbreak of food poisoning described here is of interest in several ways. So many employees reported ill in a short space of time that the plant dispensary facilities were severely taxed. Assistance was obtained from the Emergency Medical Service of the Civilian Defence Organization, ambulance service and hospitalization being quickly arranged. Preliminary treatment consisting of evacuation of the stomach and administration of morphine to the desperately ill was given at the plant.

The outbreak involved 81 employees. Symptoms began 2½ to 3 hours after ingestion of the evening meal and lasted through the night. Minor complaints continued for 2 to 3 weeks in many cases, but 60 per cent of those affected returned to work after the first week and the majority within 17 days. Haemolytic staphylococcus was isolated from the vomitus in a large proportion of those examined and in a few instances from the stool. All the patients had had their evening meal in one of the several plant dining-rooms and the one food eaten in common was corned beef. This meat had been prepared in the main kitchen and distributed to the various dining-rooms in the morning. No cases followed its use at the noon meal. The left-over meat was served again for the evening meal. Refrigeration between the two meals was probably not satisfactory at this one dining-room. Examination of employees revealed that one member of the kitchen staff who had handled the meat, had a finger infection from which haemolytic staphylococcus was obtained.

Recommendations stemming from this experience were that in any large eating establishment a daily inspection of the hands and arms of the food-handlers and an enquiry as to the presence of pimples, boils or any infection on other parts of the body should be made by someone in authority. Adequate refrigeration should be provided and adhered to. Finally an Emergency Medical Service, of invaluable service in such catastrophies, should be set up in all sizeable communities.

Benjamin J. Slater and John L. Norris, Am. J. Pub. Health, 1944, 34:855.

Salmonellosis as a Public-Health Problem in Wartime

THIS study of Salmonella infections was made in Massachusetts and begun in 1937. Cases totalled 811, of which 356 were epidemic, 408 sporadic and 47 discovered accidentally. The epidemic cases occurred in 17 outbreaks, 11 being food-borne and 6 of contact origin. Seven varieties of Salmonella organisms were identified in these epidemic cases but all the food-borne epidemics were due to either *S. typhimurium* or *S. paratyphi* B. Investigation of 295 sporadic cases revealed 113 additional infections among the contacts, 59 per cent of which were subclinical. Among the sporadic cases 4 Salmonella types, including *S. typhimurium* and *S. paratyphi* B, accounted for the majority of the cases. Seasonal incidence was typical, with the greatest number of cases occurring in the summer. Susceptibility appeared to be greater in the first decade of life, particularly in the case of *S. typhimurium*.

Both convalescents and subclinical cases continue to harbour the infecting organisms for long periods. On stool culture, 45 per cent were positive in the 4th week after onset and 11 per cent in the 10th week. Positive stools persisted longest in the very young. Fifteen permanent carriers developed among the 811 cases, 12 of them harbouring *S. paratyphi* B.

From the observations made in this study in regard to the carrier state, the occurrence of sporadic cases, subclinical infections, unrecognized and unreported cases and instances of case-to-case spread, it is felt that the importance of animal and avian sources has been overemphasized and that transmission may well be largely from human to human directly or indirectly. Salmonella cases should be kept

under observation as long as they remain infectious and should not be permitted to handle food, and permanent carriers should be recorded. To this end, Salmonellosis should be made a notifiable disease.

A. D. Rubenstein, Roy F. Feemster and Helen M. Smith, Am. J. Pub. Health, 1944, 34:841.

A Fly-Borne Bacillary Dysentery Epidemic in a Large Military Organization

THE outbreak of dysentery discussed in this article occurred at an army camp in the southern United States and totalled 1,557 cases. Rectal swab cultures, undertaken about midway through the epidemic, were obtained from all these individuals and 24.6 per cent were positive for Shigella organisms. Of these positives, 91.6 per cent showed the same organism, Shigella paradysenteriae, Boyd 88. The epidemic appeared to be fly-borne and increased in intensity as the fly population increased in density. Out of 292 lots of flies tested, 9 were positive for the above organism. The source of contamination for the flies was improperly operated straddle-trench latrines. Flies collected from closed latrines were negative on culture. One unit which was sent away from the bivouac area for training was free of further cases of dysentery after 48 hours. The epidemic subsided as fly-control measures took effect.

Two groups comprising 112 and 132 convalescent carriers were given sulfaguanidine and sulfasuxidine respectively, a third group of 60 serving as untreated controls. Subsequent cultures showed the carrier state to be relieved by either drug while the controls showed little change.

Dwight M. Kuhns and Theodore G. Anderson, Am. J. Pub. Health, 1944, 34:750.

Meningococcaemia without Meningitis; A Study Made at the Station Hospital, Fort George G. Meade, Maryland

ELEVEN case histories are presented of patients with meningococcaemia without meningitis, and the difficulties and mistakes in diagnosis are discussed. The most helpful sign in arriving at a diagnosis was the skin eruption which was present in 10 of the 11 cases. A careful description of the type of rash encountered is given. The second outstanding characteristic of the syndrome was joint and muscle pain. This has led on many occasions to confusion with rheumatic fever. Headache was a symptom in all cases and a major one in 7. Spinal taps failed to reveal significant cell counts and meningococci were not present.

All these cases were treated with sulfadiazine. Recovery was rapid and without sequelae. The rash usually began to disappear within 24 hours of starting the drug and cleared entirely in several days. The diagnosis was made in all these cases within two weeks of the onset of symptoms. Greater delay in diagnosis might have resulted in the development of meningitis in some of the 11.

Harold W. Potter, Roger D. Reid, and Lewis H. Bronstein, Ann. Int. Med., 1944, 21:2, 200.

Amoebiasis: Analytical Study of the Cases Admitted to a Philadelphia Hospital During the Last 5 Decades

IN this review of amoebiasis, it is pointed out that only 32 cases of the disease were diagnosed at the Hospital of the University of Pennsylvania in the past 5 decades. In contrast to this, studies of special groups, students, food-handlers and inmates and employees of an institution for the aged in Philadelphia, showed 5 to 10 per cent to be harbouring the parasite. The possibility of an increased incidence of amoebiasis after the war, with servicemen returning from abroad, is very real. Increased awareness of the disease by physicians, and stool examinations by competent parasitologists in all cases of diarrhoea, will be necessary for diagnosis and control of the disease.

Symptomatology and physical findings, laboratory observations and treatment are discussed and three case histories presented.

R. S. Diaz-Rivers and Edwin A. Rasberry, Am. J. Med. Sci., 1944, 207:754.

Prevention of Jaundice Resulting from Anti-Syphilitic Treatment

AN experiment is described in which an attempt was made to test the hypothesis that jaundice is spread by syringes. A group of syphilitic patients received intravenous injections by a rigidly aseptic technique which included a fresh, dry, sterilized syringe for

each injection. Service conditions rendered it impossible to obtain a control group strictly comparable in all respects. In lieu of this a comparison of results was made between the experimental group above and a considerable number of patients treated by the ordinary technique which involves the use of syringes rinsed out but not sterilized between injections.

In the experimental group 36 patients were treated for 4 months with only 1 case of jaundice and the treatment of 18 of these was continued for over 6 months without further cases. Among 67 controls there were 25 cases (37 per cent) of jaundice at the end of 4 months and this rose to 38 (68 per cent) among 56 cases kept on treatment for 6 months.

These results strongly suggest that the infective agent was transmitted by improperly sterilized syringes, though this is not necessarily the only method. A "closed method" of treatment, such as is described here, designed to eliminate possible transfer of infection from patient to patient is strongly advocated.

M. H. Salamen, A. J. King, D. I. Williams, and C. S. Nicol, Lancet, 1944, II:7.

Trichinella Skin Tests in Patients in General Hospitals and Tuberculosis Sanatoria

THIS study was conducted in North Carolina on 700 hospital and sanatorium patients of whom 10 per cent were found positive to the skin test with trichinella antigen. A previous study in this area by post-mortem examination showed an incidence of only 2.8 per cent. Similar discrepancies between the results obtained by skin-testing and by autopsy methods have been reported by other workers. Such a difference is not unexpected as the skin test may be positive whether the infestation is light or heavy, or the larvae dead or alive.

The incidence found by skin test in this study was greater in Negroes and in males, but not significantly so. There was no essential difference between urban and rural groups. Tests in 2 tuberculosis sanatoria showed 14.3 per cent positives as compared with 7.1 per cent positives in 2 general hospitals. This difference, which is significant, is not readily explained. It could be due to unrecognized or subclinical epidemics in the former institutions or to an increased reactivity of tuberculosis patients. The latter explanation is not in keeping with any known facts.

S. F. Horne and George T. Harrell, Am. J. Med. Sci., 1944, 207:759.

Epidemiology of Infective Hepatitis

OBSERVATIONS and experiments were made regarding the mode of transmission of the infective agent of jaundice in groups of patients undergoing arsenical treatment for syphilis. It was readily established that the jaundice was not due to the neo-arsphenamine. Clear-cut evidence was obtained that the infection was transmitted by means of syringes which were not sterilized but merely washed out between injections. Blood aspirated into these syringes to prove that the needle was in the vein would account for the presence and transmission of the virus.

Three orderlies and three laboratory assistants who had not received neo-arsphenamine and had not received any injections from unsterile syringes also developed jaundice. They were engaged in the handling of blood and serum from syphilitic patients, some of whom were incubating hepatitis, and it was felt that contamination of their hands with entrance of the virus through minute skin abrasions could account for their infections.

Cases of jaundice occurring in a sanatorium were investigated. The one common factor in these cases was a monthly withdrawal of blood for sedimentation tests. The syringes used were washed out but not sterilized between injections. Syringe-transmission appeared to account for these infections. The onset of the disease correlated with the bleeding intervals and supported this view.

A close study of the records of the cases from the above groups showed an incubation period of approximately 12 weeks. An attempt was made to determine the period during which the blood was infectious. This period appeared to extend from 3 to 4 weeks after the onset of the incubation period up to at least 9 weeks but definite limits could not be determined from the data, and evidence as to infectiousness during frank jaundice was not obtained.

It is suggested that the infective jaundice studied here is the same as that following injections of yellow-fever vaccine containing dried human plasma, the incubation period for which is 2-4 months.

The author reviews the problem of epidemic

infection hepatitis as it occurs in peace and war conditions and experimentally and is led to conclude that the incubation period is more likely 3 months than the 1 month usually stated and that transfer of infection by some form of subcutaneous injection is more likely than infection by faeces or droplets. Circumstantial evidence points to transfer of infection by some variety or varieties of biting insect, possibly the bedbug. The disease appears to be of the same type as homologous serum jaundice.

H. L. Sheehan, Lancet, 1944, II:8.

The Prevention of Respiratory Tract Bacterial Infections

RESPIRATORY infections and their sequelæ, chiefly due to hæmolytic streptococci, have constituted a most serious problem in United States naval training centres since the start of the war. Interference with training, man-hours lost, cost of illness and pensions and personnel required to care for those affected were so great in addition to considerations of general welfare that an extensive study and program of sulfadiazine prophylaxis was undertaken. The work was carried forward by expert teams of epidemiologists. The effectiveness of mass prophylaxis was so manifest within 3 months that untreated controls in most groups were discontinued and the program expanded to include some 50 camps. In all about 250,000 naval trainees received prophylactic doses of sulfadiazine continuously from December, 1943, to April, 1944. The present report deals with 30,000 of these men at 3 camps.

At the first camp sulfadiazine prophylaxis, 1 Gm. daily, was instituted for all hands during a severe streptococcic outbreak. This resulted in a precipitous decline in streptococcic infections and was followed by a striking fall in the incidence of rheumatic fever. The reductions experienced were not in keeping with the picture of the previous year and were not observed at other camps in the same district where sulfonamide prophylaxis was not in use.

In the second camp (5,000 men) one-half of the complement was placed on sulfadiazine in the face of a rising incidence of streptococcic infections. An immediate abrupt decline in morbidity occurred in this treated group, whereas the incidence in the control half continued to rise for a further period.

In the third camp one-half of the men were placed on 0.5 Gm. of the sulfadiazine daily starting in November, 1943, the second half serving as controls. Sick-call visits for respiratory symptoms in the untreated group were twice that for the treated, while bed care for the former was 3 times as great. In the untreated group frank streptococcic infections were 24 times as frequent as in the treated group. On March 1, 1944, both groups were placed on 1 Gm. of the drug daily and in approximately 2 weeks the morbidity experience of the previously untreated group was similar to that of the treated.

Evanescent drug rashes occurred in 0.5 per cent but sensitization to the drug as a result of the prolonged course did not occur. Dangerous constitutional reactions were observed in 0.01 per cent. No evidence was found of the development of drug fastness by the respiratory pathogens.

The program and study demonstrated that, in the amounts used, sulfadiazine served to check a well-advanced streptococcic epidemic, to check a streptococcic outbreak at its onset and to protect 85 per cent of susceptible recruits from implantation with bacterial respiratory pathogens including hæmolytic streptococcus.

Alvin F. Coburn, J.A.M.A., 1944, 126: 88.